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(54) Title: HUMAN POTASSIUM CHANNEL GENES			
(57) Abstract Methods for isolating <i>K+Hnov</i> genes are provided. The <i>K+Hnov</i> nucleic acid compositions find use in identifying homologous or related proteins and the DNA sequences encoding such proteins; in producing compositions that modulate the expression or function of the protein; and in studying associated physiological pathways. In addition, modulation of the gene activity <i>in vivo</i> is used for prophylactic and therapeutic purposes, such as identification of cell type based on expression, and the like.			

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HUMAN POTASSIUM CHANNEL GENES

INTRODUCTION

Background

5 Ion channels are multi-subunit, membrane bound proteins critical for maintenance of cellular homeostasis in nearly all cell types. Channels are involved in a myriad of processes including modulation of action potentials, regulation of cardiac myocyte excitability, heart rate, vascular tone, neuronal signaling, activation and proliferation of T-cells, and insulin secretion from
10 pancreatic islet cells. In humans, ion channels comprise extended gene families with hundreds, or perhaps thousands, of both closely related and highly divergent family members. The majority of known channels regulate the passage of sodium (Na^+), chloride (Cl^-), calcium (Ca^{++}) and potassium (K^+) ions across the cellular membrane.

15 Given their importance in maintaining normal cellular physiology, it is not surprising that ion channels have been shown to play a role in heritable human disease. Indeed, ion channel defects are involved in predisposition to epilepsy, cardiac arrhythmia (long QT syndrome), hypertension (Bartter's syndrome), cystic fibrosis, (defects in the CFTR chloride channel), several skeletal muscle disorders
20 (hyperkalemic periodic paralysis, paramyotonia congenita, episodic ataxia) and congenital neural deafness (Jervell-Lange-Nielson syndrome), amongst others.

The potassium channel gene family is believed to be the largest and most diverse ion channel family. K^+ channels have critical roles in multiple cell types and pathways, and are the focus of significant investigation. Four human
25 conditions, episodic ataxia with myokymia, long QT syndrome, epilepsy and Bartter's syndrome have been shown to be caused by defective K^+ ion channels. As the K^+ channel family is very diverse, and given that these proteins are critical components of virtually all cells, it is likely that abnormal K^+ channels will be involved in the etiology of additional renal, cardiovascular and central nervous
30 system disorders of interest to the medical and pharmaceutical community.

The K^+ channel superfamily can be broadly classified into groups, based upon the number of transmembrane domain (TMD) segments in the mature

protein. The minK (IsK) gene contains a single TMD, and although not a channel by itself, minK associates with different K⁺ channel subunits, such as KvLQT1 and HERG to modify the activity of these channels. The inward rectifying K⁺ channels (GIRK, IRK, CIR, ROMK) contain 2 TMD domains and a highly conserved pore domain. Twik-1 is a member of the newly emerging 4TMD K⁺ channel subset. Twik-like channels (leak channels) are involved in maintaining the steady-state K⁺ potentials across membranes and therefore the resting potential of the cell near the equilibrium potential for potassium (Duprat *et al.* (1997) EMBO J 16(17):5464-5471). These proteins are particularly intriguing targets for therapeutic regulation.

The 6TMD, or Shaker-like channels, presently comprise the largest subset of known K⁺ channels. The slopoke (slo) related channels, or Ca⁺⁺ regulated channels apparently have either 10 TMD, or 6 TMD with 4 additional hydrophobic domains.

Four transmembrane domain, tandem pore domain K⁺ channels (4T/2P channels) represent a new family of potassium selective ion channels involved in the control of background membrane conductances. In mammals, five channels fitting the 4T/2P architecture have been described: TWIK, TREK, TASK-1, TASK-2 and TRAAK. The 4T/2P channels all have distinct characteristics, but are all thought to be involved in maintaining the steady-state K⁺ potentials across membranes and therefore the resting potential of the cell near the equilibrium potential for potassium (Duprat *et al.* (1997) EMBO J 16(17):5464-5471). These proteins are particularly intriguing targets for therapeutic regulation. Within this group, TWIK-1, TREK-1 and TASK-1 and TASK-2 are widely distributed in many different tissues, while TRAAK is present exclusively in brain, spinal cord and retina. The 4T/2P channels have different physiologic properties; TREK-1 channels, are outwardly rectifying (Fink *et al.* (1996) EMBO J 15(24):6854-62), while TWIK-1 channels, are inwardly rectifying (Lesage *et al.* (1996) EMBO J 15(5):1004-11. TASK channels are regulated by changes in PH while TRAAK channels are stimulated by arachidonic acid (Reyes *et al.* (1998) JBC 273(47):30863-30869).

The degree of sequence homology between different K⁺ channels is substantial. At the amino acid level, there is about 40% similarity between

different human genes, with distinct regions having higher homology, specifically the pore domain. It has been estimated that the K⁺ channel gene family contains approximately 10²-10³ individual genes. Despite the large number of potential genes, an analysis of public sequence databases and the scientific literature
5 demonstrates that only a small number, approximately 20-30, have been identified. This analysis suggests that many of these important genes remain to be identified.

Potassium channels are involved in multiple different processes and are important regulators of homeostasis in nearly all cell types. Their relevance to
10 basic cellular physiology and role in many human diseases suggests that pharmacological agents could be designed to specific channel subtypes and these compounds then applied to a large market (Bulman, D.E. (1997) Hum Mol Genet 6:1679-1685; Ackerman, M.J. and Clapham D.E. (1997) NEJM 336:1575-1586, Curran, M.E. (1998) Current Opinion in Biotechnology 9:565-572). The
15 variety of therapeutic agents that modulate K⁺ channel activity reflects the diversity of physiological roles and importance of K⁺ channels in cellular function. A difficulty encountered in therapeutic use of therapeutic agents that modify K⁺ channel activity is that the presently available compounds tend to be non-specific and elicit both positive and negative responses, thereby reducing clinical efficacy.
20 To facilitate development of specific compounds it is desirable to have further characterize novel K⁺ channels for use in *in vitro* and *in vivo* assays.

Relevant Literature

A large body of literature exists in the general area of potassium channels.
25 A review of the literature may be found in the series of books, "The Ion Channel Factsbook", volumes 1-4, by Edward C. Conley and William J. Brammar, Academic Press. An overview is provided of: extracellular ligand-gated ion channels (ISBN: 0121844501), intracellular ligand-gated channels (ISBN: 012184451X), Inward rectifier and intercellular channels (ISBN: 0121844528),
30 and voltage gated channels (ISBN: 0121844536). Hille, B. (1992) "Ionic Channels of Excitable Membranes", 2nd Ed. Sunderland MA:Sinauer Associates, also reviews potassium channels.

Jan and Jan (1997) Annu. Rev. Neurosci. **20**:91-123 review cloned potassium channels from eukaryotes and prokaryotes. Ackerman and Clapham (1997) N. Engl. J. Med. **336**:1575-1586 discuss the basic science of ion channels in connection with clinical disease. Bulman (1997) Hum. Mol. Genet. **6**:1679-1685 describe some phenotypic variation in ion channel disorders.

Stephan *et al.* (1994) Neurology **44**:1915-1920 describe a pedigree segregating a myotonia with muscular hypertrophy and hyperirritability as an autosomal dominant trait (rippling muscle disease, Ricker *et al.* (1989) Arch. Neurol. **46**:405-408). Electromyography demonstrated that mechanical stimulation provoked electrically silent contractions. The responsible gene was localized to the distal end of the long arm of chromosome 1, in a 12-cM region near D1S235.

Type II pseudohypoaldosteronism is the designation used for a syndrome of chronic mineralocorticoid-resistant hyperkalemia with hypertension. The primary abnormality in type II PHA is thought to be a specific defect of the renal secretory mechanism for potassium, which limits the kaliuretic response to, but not the sodium and chloride reabsorptive effect of, mineralocorticoid. By analysis of linkage in families with autosomal dominant transmission, Mansfield *et al.* (1997) Nature Genet. **16**:202-205 demonstrated locus heterogeneity of the trait, with linkage of the PHA2 gene to 1q31-q42 and 17p11-q21.

Sequences of four transmembrane, two pore potassium channels have been previously described. Reyes *et al.* (1998) J Biol Chem **273**(47):30863-30869 discloses a pH sensitive channel. As with the related TASK-1 and TRAAK channels, the outward rectification is lost at high external K⁺ concentration. The TRAAK channel is described by Fink *et al.* (1998) EMBO J **17**(12):3297-308. A cardiac two-pore channel is described in Kim *et al.* (1998) Circ Res **82**(4):513-8. An open rectifier potassium channel with two pore domains in tandem and having a postsynaptic density protein binding sequence at the C terminal was cloned by Leonoudakis *et al.* (1998) J Neurosci **18**(3):868-77.

The electrophysiological properties of Task channels are of interest, (Duprat *et al.* (1997) EMBO J **16**:5464-71). TASK currents are K⁺-selective, instantaneous and non-inactivating. They show an outward rectification when external [K⁺] is low, which is not observed for high [K⁺]_{out}, suggesting a lack of

intrinsic voltage sensitivity. The absence of activation and inactivation kinetics as well as voltage independence are characteristic of conductances referred to as leak or background conductances. TASK is very sensitive to variations of extracellular pH in a narrow physiological range, a property probably essential for its physiological function, and suggests that small pH variations may serve a communication role in the nervous system.

SUMMARY OF THE INVENTION

Isolated nucleotide compositions and sequences are provided for *K+Hnov* genes. The *K+Hnov* nucleic acid compositions find use in identifying homologous or related genes; in producing compositions that modulate the expression or function of its encoded proteins; for gene therapy; mapping functional regions of the proteins; and in studying associated physiological pathways. In addition, modulation of the gene activity *in vivo* is used for prophylactic and therapeutic purposes, such as treatment of potassium channel defects, identification of cell type based on expression, and the like.

DESCRIPTION OF THE SPECIFIC EMBODIMENTS

Nucleic acid compositions encoding *K+Hnov* polypeptides are provided. They are used in identifying homologous or related genes; in producing compositions that modulate the expression or function of the encoded proteins; for gene therapy; mapping functional regions of the proteins; and in studying associated physiological pathways. The *K+Hnov* gene products are members of the potassium channel gene family, and have high degrees of homology to known potassium channels. The encoded polypeptides may be alpha subunits, which form the functional channel, or accessory subunits that act to modulate the channel activity.

CHARACTERIZATION OF *K+HNOV*

The sequence data predict that the provided *K+Hnov* genes encode potassium channels. Table 1 summarizes the DNA sequences, corresponding SEQ ID NOs, chromosomal locations, and polymorphisms. The provided

sequences may encode a predicted K⁺ channel, e.g. voltage gated, inward rectifier, etc.; or a modulatory subunit.

Electrophysiologic characterization of ion channels is an important part of understanding channel function. Full length ion channel cDNAs may be
5 combined with proper vectors to form expression constructs of each individual channel. Functional analyses of expressed channels can be performed in heterologous systems, or by expression in mammalian cell lines. For expression analyses in heterologous systems such as *Xenopus* oocytes, synthetic mRNA is made through *in vitro* transcription of each channel construct. mRNA is then
10 injected, singly or in combination with interacting channel subunit mRNAs, into prepared oocytes and the cells allowed to express the channel for several days. Oocytes expressing the channel of interest are then analyzed by whole cell voltage clamp and patch clamp techniques.

To determine the properties of each channel when expressed in
15 mammalian cells expression vectors specific to this type of analyses may be constructed and the resultant construct used to transform the target cells (for example human embryonic kidney (HEK) cells). Both stable and transiently expressing lines may be studied using whole cell voltage clamp and patch clamp techniques. Data obtained from EP studies includes, but is not limited to: current
20 profiles elicited by depolarization and hyperpolarization, current-voltage (I-V) relationships, voltage dependence of activation, biophysical kinetics of channel activation, deactivation, and inactivation, reversal potential, ion selectivity, gating properties and sensitivity to channel antagonists and agonists.

Heterologous or mammalian cell lines expressing the novel channels can
25 be used to characterize small molecules and drugs which interact with the channel. The same experiments can be used to assay for novel compounds which interact with the expressed channels.

In many cases the functional ion channel formed by K⁺ H₂O₂ polypeptides will be heteromultimers. Heteromultimers are known to form between different
30 voltage gated, outward rectifying potassium channel α subunits, generally comprising four subunits, and frequently associated with auxiliary, β subunits. Typically such α subunits share a six-transmembrane domain structure (S1-S6),

with one highly positively charged domain (S4) and a pore region situated between S5 and S6. Examples of such subunits are K+Hnov4, K+Hnov9, and K+Hnov12. Channels are also formed by multimerization of subunits of the two transmembrane and one pore architecture. It is predicted that two subunits of
5 K+Hnov49 or K+Hnov59 will be required to form a functional channel.

Heteromultimers of greatest interest are those that form between subunits expressed in the same tissues, and are a combination of subunits from the same species. In addition, the formation of multimers between the subject polypeptides and subunits that form functional channels are of particular interest. The resulting
10 channel may have decreased or increased conductance relative to a homomultimer, and may be altered in response to beta subunits or other modulatory molecules.

Known voltage gated K⁺ channel α subunits include Kv1.1-1.8 (Gutman *et al.* (1993) *Sem. Neurosci.* 5:101-106); Kv2.1-2.2; Kv3.1-3.4; Kv4.1-4.3; Kv5.1; Kv6.1; Kv7.1; Kv8.1; Kv9.1-9.2. The subunits capable of forming ion inducing
15 channels include all of those in the Kv1 through Kv4; and Kv7 families. The Kv5.1, Kv6.1, Kv8.1 and Kv9.1-9.2 subunits may be electrically silent, but functional in modifying the properties in heteromultimers.

TABLE 1

Name	cDNA SEQ	Protein SEQ	Polymorphisms	Chromosome Position	Channel Type
K+Hnov1	SEQ ID NO:1	SEQ ID NO:2	Alternative poly(A) tail: 1236, 2395	2q37	ATP-sensitive inward rectifying
K+Hnov4	SEQ ID NO:3	SEQ ID NO:4	A312C T335C A377G T344C A401G CA410-411GG (Ala/Thr)	unknown	Voltage gated K+ channel
K+Hnov6	SEQ ID NO:5	SEQ ID NO:6		2p23	Delayed rectifying K+ channel
K+Hnov9	SEQ ID NO:7	SEQ ID NO:8	Alternative poly(A) tail: 2304	8q23	Voltage gated K+ channel
K+Hnov12	SEQ ID NO:9	SEQ ID NO:10	C321T (Pro/Leu) A375G (Glu/Gly) C407T (Leu/Phe)	Xp21	Voltage gated K+ channel
K+Hnov15	SEQ ID NO:11	SEQ ID NO:12	Alternative poly(A) tail: 1427 A689G (Gly/Arg)	13q14	modulatory subunit
K+Hnov27	SEQ ID NO:13	SEQ ID NO:14	T365A (Ile/Asn)	18q12	modulatory subunit
K+Hnov2	SEQ ID NO:15	SEQ ID NO:16	N/A	N/A	4 transmembrane domain, 2 pore domain K+ channel

K+Hnov 11	SEQ ID NO:17	SEQ ID NO:18	N/A	N/A	Human ortholog of murine gene, 6 transmembrane domains, voltage gated, delayed rectifier K+ channel
K+Hnov 14	SEQ ID NO:19	SEQ ID NO:20	C3168T	12q14	6 transmembrane domain, voltage gated K+ channel
K+Hnov28	SEQ ID NO:21-24	SEQ ID NO:25	4 alternative 5' splices	3q29	Modulatory subunit
K+Hnov42	SEQ ID NO:26	SEQ ID NO:27	G1162A; T1460A; T2496A	8q11	Homology to K+ channel protein of <i>C. elegans</i>
K+Hnov44	SEQ ID NO:28-29	SEQ ID NO:30	N/A	22p13	beta-subunit.
K'Hnov49	SEQ ID NO:80	SEQ ID NO:81	(ATCT) _n repeats in the 3' UTR sequence, starting at position 2186	1q41	4T/2P channel; linked to the disease loci for rippling muscle disease 1 (RMD1), and type II pseudohypoparathyroidism
K'Hnov59	SEQ ID NO:82	SEQ ID NO:83	N/A	chr19	4T/2P channel

K+Hnov NUCLEIC ACID COMPOSITIONS

As used herein, the term "K+Hnov" is generically used to refer to any one of the provided genetic sequences listed in Table 1. Where a specific K+Hnov sequence is intended, the numerical designation, e.g. K49 or K59, will be added.

- 5 Nucleic acids encoding *K+Hnov* potassium channels may be cDNA or genomic DNA or a fragment thereof. The term "*K+Hnov* gene" shall be intended to mean the open reading frame encoding any of the provided *K+Hnov* polypeptides, introns, as well as adjacent 5' and 3' non-coding nucleotide sequences involved in the regulation of expression, up to about 20 kb beyond the coding region, but
- 10 possibly further in either direction. The gene may be introduced into an appropriate vector for extrachromosomal maintenance or for integration into a host genome.

The term "cDNA" as used herein is intended to include all nucleic acids that share the arrangement of sequence elements found in native mature mRNA species, where sequence elements are exons and 3' and 5' non-coding regions. Normally mRNA species have contiguous exons, with the intervening introns, when present, removed by nuclear RNA splicing, to create a continuous open reading frame encoding a K+Hnov protein.

A genomic sequence of interest comprises the nucleic acid present

20 between the initiation codon and the stop codon, as defined in the listed sequences, including all of the introns that are normally present in a native chromosome. It may further include the 3' and 5' untranslated regions found in the mature mRNA. It may further include specific transcriptional and translational regulatory sequences, such as promoters, enhancers, etc., including about 1 kb,

25 but possibly more, of flanking genomic DNA at either the 5' or 3' end of the transcribed region. The genomic DNA may be isolated as a fragment of 100 kbp or smaller; and substantially free of flanking chromosomal sequence. The genomic DNA flanking the coding region, either 3' or 5', or internal regulatory sequences as sometimes found in introns, contains sequences required for

30 proper tissue and stage specific expression.

The sequence of the 5' flanking region may be utilized for promoter elements, including enhancer binding sites, that provide for developmental regulation in tissues where *K+Hnov* genes are expressed. The tissue specific expression is useful for determining the pattern of expression, and for providing promoters that mimic the native pattern of expression. Naturally occurring polymorphisms in the promoter regions are useful for determining natural variations in expression, particularly those that may be associated with disease.

Alternatively, mutations may be introduced into the promoter regions to determine the effect of altering expression in experimentally defined systems.

Methods for the identification of specific DNA motifs involved in the binding of transcriptional factors are known in the art, e.g. sequence similarity to known binding motifs, gel retardation studies, etc. For examples, see Blackwell *et al.* (1995) Mol Med 1: 194-205; Mortlock *et al.* (1996) Genome Res. 6: 327-33; and Joulin and Richard-Foy (1995) Eur J Biochem 232: 620-626.

The regulatory sequences may be used to identify *cis* acting sequences required for transcriptional or translational regulation of *K+Hnov* expression, especially in different tissues or stages of development, and to identify *cis* acting sequences and *trans* acting factors that regulate or mediate *K+Hnov* expression. Such transcription or translational control regions may be operably linked to a *K+Hnov* gene in order to promote expression of wild type or altered *K+Hnov* or other proteins of interest in cultured cells, or in embryonic, fetal or adult tissues, and for gene therapy.

The nucleic acid compositions of the subject invention may encode all or a part of the subject polypeptides. Double or single stranded fragments may be obtained of the DNA sequence by chemically synthesizing oligonucleotides in accordance with conventional methods, by restriction enzyme digestion, by PCR amplification, etc. For the most part, DNA fragments will be of at least 15 nt, usually at least 18 nt or 25 nt, and may be at least about 50 nt. Such small DNA fragments are useful as primers for PCR, hybridization screening probes, etc. Larger DNA fragments, i.e. greater than 100 nt are useful for production of the encoded polypeptide. For use in amplification reactions, such as PCR, a pair of

primers will be used. The exact composition of the primer sequences is not critical to the invention, but for most applications the primers will hybridize to the subject sequence under stringent conditions, as known in the art. It is preferable to choose a pair of primers that will generate an amplification product of at least
5 about 50 nt, preferably at least about 100 nt. Algorithms for the selection of primer sequences are generally known, and are available in commercial software packages. Amplification primers hybridize to complementary strands of DNA, and will prime towards each other.

The *K+Hnov* genes are isolated and obtained in substantial purity,
10 generally as other than an intact chromosome. Usually, the DNA will be obtained substantially free of other nucleic acid sequences that do not include a *K+Hnov* sequence or fragment thereof, generally being at least about 50%, usually at least about 90% pure and are typically "recombinant", i.e. flanked by one or more nucleotides with which it is not normally associated on a naturally occurring
15 chromosome.

The DNA may also be used to identify expression of the gene in a biological specimen. The manner in which one probes cells for the presence of particular nucleotide sequences, as genomic DNA or RNA, is well established in the literature and does not require elaboration here. DNA or mRNA is isolated
20 from a cell sample. The mRNA may be amplified by RT-PCR, using reverse transcriptase to form a complementary DNA strand, followed by polymerase chain reaction amplification using primers specific for the subject DNA sequences. Alternatively, the mRNA sample is separated by gel electrophoresis, transferred to a suitable support, e.g. nitrocellulose, nylon, etc., and then probed with a
25 fragment of the subject DNA as a probe. Other techniques, such as oligonucleotide ligation assays, *in situ* hybridizations, and hybridization to DNA probes arrayed on a solid chip may also find use. Detection of mRNA hybridizing to the subject sequence is indicative of *K+Hnov* gene expression in the sample.

The sequence of a *K+Hnov* gene, including flanking promoter regions and
30 coding regions, may be mutated in various ways known in the art to generate targeted changes in promoter strength, sequence of the encoded protein, etc.

The DNA sequence or protein product of such a mutation will usually be substantially similar to the sequences provided herein, *i.e.* will differ by at least one nucleotide or amino acid, respectively, and may differ by at least two but not more than about ten nucleotides or amino acids. The sequence changes may be substitutions, insertions or deletions. Deletions may further include larger changes, such as deletions of a domain or exon. Other modifications of interest include epitope tagging, *e.g.* with the FLAG system, HA, *etc.* For studies of subcellular localization, fusion proteins with green fluorescent proteins (GFP) may be used.

Techniques for *in vitro* mutagenesis of cloned genes are known. Examples of protocols for site specific mutagenesis may be found in Gustin *et al.*, *Biotechniques* 14:22 (1993); Barany, *Gene* 37:111-23 (1985); Colicelli *et al.*, *Mol Gen Genet* 199:537-9 (1985); and Prentki *et al.*, *Gene* 29:303-13 (1984). Methods for site specific mutagenesis can be found in Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual*, CSH Press 1989, pp. 15.3-15.108; Weiner *et al.*, *Gene* 126:35-41 (1993); Sayers *et al.*, *Biotechniques* 13:592-6 (1992); Jones and Winistorfer, *Biotechniques* 12:528-30 (1992); Barton *et al.*, *Nucleic Acids Res* 18:7349-55 (1990); Marotti and Tomich, *Gene Anal Tech* 6:67-70 (1989); and Zhu, *Anal Biochem* 177:120-4 (1989). Such mutated genes may be used to study structure-function relationships of K+Hnov, or to alter properties of the protein that affect its function or regulation.

Homologs and orthologs of K+Hnov genes are identified by any of a number of methods. A fragment of the provided cDNA may be used as a hybridization probe against a cDNA library from the target organism of interest, where low stringency conditions are used. The probe may be a large fragment, or one or more short degenerate primers. Nucleic acids having sequence similarity are detected by hybridization under low stringency conditions, for example, at 50°C and 6XSSC (0.9 M sodium chloride/0.09 M sodium citrate) and remain bound when subjected to washing at 55°C in 1XSSC (0.15 M sodium chloride/0.015 M sodium citrate). Sequence identity may be determined by hybridization under string nt conditions, for example, at 50°C or higher and

0.1XSSC (15 mM sodium chloride/0.15 mM sodium citrate). Nucleic acids having a region of substantial identity to the provided K+Hnov sequences, *e.g.* allelic variants, genetically altered versions of the gene, *etc.*, bind to the provided K+Hnov sequences under stringent hybridization conditions. By using probes, particularly labeled probes of DNA sequences, one can isolate homologous or related genes. The source of homologous genes may be any species, *e.g.* primate species, particularly human; rodents, such as rats and mice, canines, felines, bovines, ovines, equines, yeast, nematodes, *etc.*

Between mammalian species, *e.g.* human and mouse, homologs have substantial sequence similarity, *i.e.* at least 75% sequence identity between nucleotide sequences, in some cases 80 or 90% sequence identity, and may be as high as 95% sequence identity between closely related species. Sequence similarity is calculated based on a reference sequence, which may be a subset of a larger sequence, such as a conserved motif, coding region, flanking region, *etc.*

A reference sequence will usually be at least about 18 nt long, more usually at least about 30 nt long, and may extend to the complete sequence that is being compared. Algorithms for sequence analysis are known in the art, such as BLAST, described in Altschul et al. (1990), J. Mol. Biol. 215:403-10. In general, variants of the invention have a sequence identity greater than at least about 65%, preferably at least about 75%, more preferably at least about 85%, and may be greater than at least about 90% or more as determined by the Smith-Waterman homology search algorithm as implemented in MPSRCH program (Oxford Molecular). Exemplary search parameters for use with the MPSRCH program in order to identify sequences of a desired sequence identity are as follows: gap open penalty: 12; and gap extension penalty: 1.

K+HNOV POLYPEPTIDES

The subject nucleic acid sequences may be employed for producing all or portions of K+Hnov polypeptides. For expression, an expression cassette may be employed. The expression vector will provide a transcriptional and translational initiation region, which may be inducible or constitutive, where the coding region

is operably linked under the transcriptional control of the transcriptional initiation region, and a transcriptional and translational termination region. These control regions may be native to a *K+Hnov* gene, or may be derived from exogenous sources.

5 The peptide may be expressed in prokaryotes or eukaryotes in accordance with conventional ways, depending upon the purpose for expression. For large scale production of the protein, a unicellular organism, such as *E. coli*, *B. subtilis*, *S. cerevisiae*, insect cells in combination with baculovirus vectors, or cells of a higher organism such as vertebrates, particularly mammals, e.g. COS 7 cells,
10 may be used as the expression host cells. In some situations, it is desirable to express the *K+Hnov* gene in eukaryotic cells, where the K+Hnov protein will benefit from native folding and post-translational modifications. Small peptides can also be synthesized in the laboratory. Peptides that are subsets of the complete *K+Hnov* sequence may be used to identify and investigate parts of the
15 protein important for function, or to raise antibodies directed against these regions.

 Fragments of interest include the transmembrane and pore domains, the signal sequences, regions of interaction between subunits, etc. Such domains will usually include at least about 20 amino acids of the provided sequence, more
20 usually at least about 50 amino acids, and may include 100 amino acids or more, up to the complete domain. Binding contacts may be comprised of non-contiguous sequences, which are brought into proximity by the tertiary structure of the protein. The sequence of such fragments may be modified through manipulation of the coding sequence, as described above. Truncations may be
25 performed at the carboxy or amino terminus of the fragment, e.g. to determine the minimum sequence required for biological activity.

 With the availability of the protein or fragments thereof in large amounts, by employing an expression host, the protein may be isolated and purified in accordance with conventional ways. A lysate may be prepared of the expression
30 host and the lysate purified using HPLC, exclusion chromatography, gel electrophoresis, affinity chromatography, or other purification technique. The

purified protein will generally be at least about 80% pure, preferably at least about 90% pure, and may be up to and including 100% pure. Pure is intended to mean free of other proteins, as well as cellular debris.

The expressed K+Hnov polypeptides are useful for the production of antibodies, where short fragments provide for antibodies specific for the particular polypeptide, and larger fragments or the entire protein allow for the production of antibodies over the surface of the polypeptide. Antibodies may be raised to the wild-type or variant forms of K+Hnov. Antibodies may be raised to isolated peptides corresponding to specific domains, e.g. the pore domain and the transmembrane domain, or to the native protein.

Antibodies are prepared in accordance with conventional ways, where the expressed polypeptide or protein is used as an immunogen, by itself or conjugated to known immunogenic carriers, e.g. KLH, pre-S HBsAg, other viral or eukaryotic proteins, or the like. Various adjuvants may be employed, with a series of injections, as appropriate. For monoclonal antibodies, after one or more booster injections, the spleen is isolated, the lymphocytes immortalized by cell fusion, and then screened for high affinity antibody binding. The immortalized cells, i.e. hybridomas, producing the desired antibodies may then be expanded. For further description, see Monoclonal Antibodies: A Laboratory Manual, Harlow and Lane eds., Cold Spring Harbor Laboratories, Cold Spring Harbor, New York, 1988. If desired, the mRNA encoding the heavy and light chains may be isolated and mutagenized by cloning in *E. coli*, and the heavy and light chains mixed to further enhance the affinity of the antibody. Alternatives to *in vivo* immunization as a method of raising antibodies include binding to phage "display" libraries, usually in conjunction with *in vitro* affinity maturation.

K+HNOV GENOTYPING

The subject nucleic acid and/or polypeptide compositions may be used to genotyping and other analysis for the presence of polymorphisms in the sequence, or variation in the expression of the subject genes. Genotyping may be performed to determine whether a particular polymorphism is associated with

a disease state or genetic predisposition to a disease state, particularly diseases associated with defects in excitatory properties of cells, e.g. cardiac, muscle, renal and neural cells. Diseases of interest include rippling muscle disease, and type II pseudohypoaldosteronism.

5 Clinical disorders associated with K⁺ channel defects include long-QT syndrome; a congenital disorder affecting 1 in 10,000-15,000. Affected individuals have a prolonged QT interval in the electrocardiogram due to a delayed repolarization of the ventricle. Genetic linkage analyses identified two loci for long QT syndrome, LQT1, in 11p15.5 and LQT2, in 7q35-36. Positional
10 cloning techniques identified the novel K⁺ channel KvLQT1 on chromosome 11 while candidate gene analysis identified causative mutations in the HERG K⁺ channel for LQT2.

The weaver mouse exhibits several abnormal neurological symptoms, including severe ataxia, loss of granule cell neurons in the cerebellum and
15 dopaminergic cells in the substantia nigra, as well as seizures and male infertility. A G-protein-coupled K⁺ channel having a mutation in the conserved pore domain has been determined to cause the disease. The pancreatic-islet β -cell ATP-sensitive K⁺ channel (KATP) is composed of two subunits, the sulfonylurea receptor (SUR) and the inward rectifier K⁺ channel Kir6.2. Mutations in both SUR
20 and Kir6.2 have been identified in patients with persistent hyperinsulinemic hypoglycemia of infancy, which is caused by unregulated secretion of insulin.

Genotyping may also be performed for pharmacogenetic analysis to assess the association between an individual's genotype and that individual's ability to react to a therapeutic agent. Differences in target sensitivity can lead to
25 toxicity or therapeutic failure. Relationships between polymorphisms in channel expression or specificity can be used to optimize therapeutic dose administration.

Genetic polymorphisms are identified in the K⁺Hnov gene (examples are listed in table 1), e.g. the repeat variation in the 3' UTR of K49. Nucleic acids comprising the polymorphic sequences are used to screen patients for altered
30 reactivity and adverse side effects in response to drugs that act on K⁺ channels.

K+Hnov genotyping is performed by DNA or RNA sequence and/or hybridization analysis of any convenient sample from a patient, e.g. biopsy material, blood sample, scrapings from cheek, etc. A nucleic acid sample from an individual is analyzed for the presence of polymorphisms in K+Hnov, particularly those that affect the activity, responsiveness or expression of K+Hnov. Specific sequences of interest include any polymorphism that leads to changes in basal expression in one or more tissues, to changes in the modulation of K+Hnov expression, or alterations in K+Hnov specificity and/or activity.

The effect of a polymorphism in K+Hnov gene sequence on the response to a particular agent may be determined by *in vitro* or *in vivo* assays. Such assays may include monitoring during clinical trials, testing on genetically defined cell lines, etc. The response of an individual to the agent can then be predicted by determining the K+Hnov genotype with respect to the polymorphism. Where there is a differential distribution of a polymorphism by racial background, guidelines for drug administration can be generally tailored to a particular ethnic group.

Biochemical studies may be performed to determine whether a sequence polymorphism in a *K+Hnov* coding region or control regions is associated with disease, for example the association of K+Hnov 9 with idiopathic generalized epilepsy. Disease associated polymorphisms may include deletion or truncation of the gene, mutations that alter expression level, that affect the electrical activity of the channel, etc.

A number of methods are available for analyzing nucleic acids for the presence of a specific sequence. Where large amounts of DNA are available, genomic DNA is used directly. Alternatively, the region of interest is cloned into a suitable vector and grown in sufficient quantity for analysis. The nucleic acid may be amplified by conventional techniques, such as the polymerase chain reaction (PCR), to provide sufficient amounts for analysis. The use of the polymerase chain reaction is described in Saiki *et al.* (1985) Science 239:487, and a review of current techniques may be found in Sambrook *et al.* *Molecular Cloning: A Laboratory Manual*, CSH Press 1989, pp.14.2-14.33. Amplification may be used

to determine whether a polymorphism is present, by using a primer that is specific for the polymorphism. Alternatively, various methods are known in the art that utilize oligonucleotide ligation as a means of detecting polymorphisms, for examples see Riley *et al.* (1990) N.A.R. 18:2887-2890; and Delahunty *et al.* 5 (1996) Am. J. Hum. Genet. 58:1239-1246.

A detectable label may be included in an amplification reaction. Suitable labels include fluorochromes, e.g. fluorescein isothiocyanate (FITC), rhodamine, Texas Red, phycoerythrin, allophycocyanin, 6-carboxyfluorescein (6-FAM), 2',7'-dimethoxy-4',5'-dichloro-6-carboxyfluorescein (JOE), 6-carboxy-X-rhodamine 10 (ROX), 6-carboxy-2',4',7',4,7-hexachlorofluorescein (HEX), 5-carboxyfluorescein (5-FAM) or N,N,N',N'-tetramethyl-6-carboxyrhodamine (TAMRA), radioactive labels, e.g. 32P, 35S, 3H; etc. The label may be a two stage system, where the amplified DNA is conjugated to biotin, haptens, etc. having a high affinity binding partner, e.g. avidin, specific antibodies, etc., where the binding partner is 15 conjugated to a detectable label. The label may be conjugated to one or both of the primers. Alternatively, the pool of nucleotides used in the amplification is labeled, so as to incorporate the label into the amplification product.

The sample nucleic acid, e.g. amplified or cloned fragment, is analyzed by one of a number of methods known in the art. The nucleic acid may be 20 sequenced by dideoxy or other methods. Hybridization with the variant sequence may also be used to determine its presence, by Southern blots, dot blots, etc. The hybridization pattern of a control and variant sequence to an array of oligonucleotide probes immobilised on a solid support, as described in U.S. 5,445,934, or in WO95/35505, may also be used as a means of detecting the 25 presence of variant sequences. Single strand conformational polymorphism (SSCP) analysis, denaturing gradient gel electrophoresis (DGGE), mismatch cleavage detection, and heteroduplex analysis in gel matrices are used to detect conformational changes created by DNA sequence variation as alterations in electrophoretic mobility. Alternatively, where a polymorphism creates or destroys 30 a recognition site for a restriction endonuclease (restriction fragment length polymorphism, RFLP), the sample is digested with that endonuclease, and the

products size fractionated to determine whether the fragment was digested. Fractionation is performed by gel or capillary electrophoresis, particularly acrylamide or agarose gels.

In one embodiment of the invention, an array of oligonucleotides are
5 provided, where discrete positions on the array are complementary to one or more of the provided sequences, e.g. oligonucleotides of at least 12 nt, frequently 20 nt, or larger, and including the sequence flanking a polymorphic position in a K⁺Hnov sequence; coding sequences for different K⁺Hnov channels, panels of ion channels comprising one or more of the provided K⁺ channels; etc. Such an array
10 may comprise a series of oligonucleotides, each of which can specifically hybridize to a different polymorphism. For examples of arrays, see Hacia *et al.* (1996) Nature Genetics 14:441-447; Lockhart *et al.* (1996) Nature Biotechnol. 14:1675-1680; and De Risi *et al.* (1996) Nature Genetics 14:457-460.

Screening for polymorphisms in K⁺Hnov may be based on the functional or
15 antigenic characteristics of the protein. Protein truncation assays are useful in detecting deletions that may affect the biological activity of the protein. Various immunoassays designed to detect polymorphisms in K⁺Hnov proteins may be used in screening. Where many diverse genetic mutations lead to a particular disease phenotype, functional protein assays have proven to be effective
20 screening tools. The activity of the encoded K⁺Hnov protein as a potassium channel may be determined by comparison with the wild-type protein.

Antibodies specific for a K⁺Hnov may be used in staining or in immunoassays. Samples, as used herein, include biological fluids such as semen, blood, cerebrospinal fluid, tears, saliva, lymph, dialysis fluid and the like;
25 organ or tissue culture derived fluids; and fluids extracted from physiological tissues. Also included in the term are derivatives and fractions of such fluids. The cells may be dissociated, in the case of solid tissues, or tissue sections may be analyzed. Alternatively a lysate of the cells may be prepared.

Diagnosis may be performed by a number of methods to determine the
30 absence or presence or altered amounts of normal or abnormal K⁺Hnov polypeptides in patient cells. For example, detection may utilize staining of cells

or histological sections, performed in accordance with conventional methods. The antibodies of interest are added to the cell sample, and incubated for a period of time sufficient to allow binding to the epitope, usually at least about 10 minutes. The antibody may be labeled with radioisotopes, enzymes, fluorescers, chemiluminescers, or other labels for direct detection. Alternatively, a second stage antibody or reagent is used to amplify the signal. Such reagents are well known in the art. For example, the primary antibody may be conjugated to biotin, with horseradish peroxidase-conjugated avidin added as a second stage reagent. Alternatively, the secondary antibody conjugated to a fluorescent compound, e.g. fluorescein, rhodamine, Texas red, etc. Final detection uses a substrate that undergoes a color change in the presence of the peroxidase. The absence or presence of antibody binding may be determined by various methods, including flow cytometry of dissociated cells, microscopy, radiography, scintillation counting, etc.

15

MODULATION OF GENE EXPRESSION

The K+Hnov genes, gene fragments, or the encoded protein or protein fragments are useful in gene therapy to treat disorders associated with K+Hnov defects. Expression vectors may be used to introduce the K+Hnov gene into a cell. Such vectors generally have convenient restriction sites located near the promoter sequence to provide for the insertion of nucleic acid sequences. Transcription cassettes may be prepared comprising a transcription initiation region, the target gene or fragment thereof, and a transcriptional termination region. The transcription cassettes may be introduced into a variety of vectors, e.g. plasmid; retrovirus, e.g. lentivirus; adenovirus; and the like, where the vectors are able to transiently or stably be maintained in the cells, usually for a period of at least about one day, more usually for a period of at least about several days to several weeks.

The gene or K+Hnov protein may be introduced into tissues or host cells by any number of routes, including viral infection, microinjection, or fusion of vesicles. Jet injection may also be used for intramuscular administration, as

30

described by Furth *et al.* (1992) Anal Bi chem **205**:365-368. The DNA may be coated onto gold microparticles, and delivered intradermally by a particle bombardment device, or "gene gun" as described in the literature (see, for example, Tang *et al.* (1992) Nature **356**:152-154), where gold microprojectiles are
5 coated with the K+Hnov or DNA, then bombarded into skin cells.

Antisense molecules can be used to down-regulate expression of K+Hnov in cells. The anti-sense reagent may be antisense oligonucleotides (ODN), particularly synthetic ODN having chemical modifications from native nucleic acids, or nucleic acid constructs that express such anti-sense molecules as RNA.
10 The antisense sequence is complementary to the mRNA of the targeted gene, and inhibits expression of the targeted gene products. Antisense molecules inhibit gene expression through various mechanisms, e.g. by reducing the amount of mRNA available for translation, through activation of RNase H, or steric hindrance. One or a combination of antisense molecules may be administered,
15 where a combination may comprise multiple different sequences.

Antisense molecules may be produced by expression of all or a part of the target gene sequence in an appropriate vector, where the transcriptional initiation is oriented such that an antisense strand is produced as an RNA molecule. Alternatively, the antisense molecule is a synthetic oligonucleotide. Antisense
20 oligonucleotides will generally be at least about 7, usually at least about 12, more usually at least about 20 nucleotides in length, and not more than about 500, usually not more than about 50, more usually not more than about 35 nucleotides in length, where the length is governed by efficiency of inhibition, specificity, including absence of cross-reactivity, and the like. It has been found that short
25 oligonucleotides, of from 7 to 8 bases in length, can be strong and selective inhibitors of gene expression (see Wagner *et al.* (1996) Nature Biotechnology **14**:840-844).

A specific region or regions of the endogenous sense strand mRNA sequence is chosen to be complemented by the antisense sequence. Selection
30 of a specific sequence for the oligonucleotide may use an empirical method, where several candidate sequences are assayed for inhibition of expression of

th target gene in an *in vitro* or animal model. A combination of sequences may also be used, where several regions of the mRNA sequence are selected for antisense complementation.

Antisense oligonucleotides may be chemically synthesized by methods known in the art (see Wagner *et al.* (1993) *supra.* and Milligan *et al.*, *supra.*) Preferred oligonucleotides are chemically modified from the native phosphodiester structure, in order to increase their intracellular stability and binding affinity. A number of such modifications have been described in the literature, which alter the chemistry of the backbone, sugars or heterocyclic bases.

Among useful changes in the backbone chemistry are phosphorothioates; phosphorodithioates, where both of the non-bridging oxygens are substituted with sulfur; phosphoroamidites; alkyl phosphotriesters and boranophosphates. Achiral phosphate derivatives include 3'-O'-5'-S-phosphorothioate, 3'-S-5'-O-phosphorothioate, 3'-CH₂-5'-O-phosphonate and 3'-NH-5'-O-phosphoroamidate. Peptide nucleic acids replace the entire ribose phosphodiester backbone with a peptide linkage. Sugar modifications are also used to enhance stability and affinity. The α -anomer of deoxyribose may be used, where the base is inverted with respect to the natural β -anomer. The 2'-OH of the ribose sugar may be altered to form 2'-O-methyl or 2'-O-allyl sugars, which provides resistance to degradation without comprising affinity. Modification of the heterocyclic bases must maintain proper base pairing. Some useful substitutions include deoxyuridine for deoxythymidine; 5-methyl-2'-deoxycytidine and 5-bromo-2'-deoxycytidine for deoxycytidine. 5-propynyl-2'-deoxyuridine and 5-propynyl-2'-deoxycytidine have been shown to increase affinity and biological activity when substituted for deoxythymidine and deoxycytidine, respectively.

As an alternative to anti-sense inhibitors, catalytic nucleic acid compounds, *e.g.* ribozymes, anti-sense conjugates, *etc.* may be used to inhibit gene expression. Ribozymes may be synthesized *in vitro* and administered to the patient, or may be encoded on an expression vector, from which the ribozyme is synthesized in the targeted cell (for example, see International patent application

WO 9523225, and Beigelman et al. (1995) Nucl. Acids Res 23:4434-42).
Examples of oligonucleotides with catalytic activity are described in WO 9506764.
Conjugates of anti-sense ODN with a metal complex, e.g. terpyridylCu(II), capable
of mediating mRNA hydrolysis are described in Bashkin et al. (1995) Appl
5 Biochem Biotechnol 54:43-56.

GENETICALLY ALTERED CELL OR ANIMAL MODELS FOR K+Hnov FUNCTION

The subject nucleic acids can be used to generate transgenic animals or
site specific gene modifications in cell lines. Transgenic animals may be made
10 through homologous recombination, where the normal *K+Hnov* locus is altered.
Alternatively, a nucleic acid construct is randomly integrated into the genome.
Vectors for stable integration include plasmids, retroviruses and other animal
viruses, YACs, and the like.

The modified cells or animals are useful in the study of *K+Hnov* function
15 and regulation. For example, a series of small deletions and/or substitutions may
be made in the *K+Hnov* gene to determine the role of different transmembrane
domains in forming multimeric structures, ion channels, etc. Of interest are the
use of *K+Hnov* to construct transgenic animal models for epilepsy and other
neurological defects, where expression of K+Hnov is specifically reduced or
20 absent. Specific constructs of interest include anti-sense *K+Hnov*, which will
block K+Hnov expression, expression of dominant negative K+Hnov mutations,
etc. One may also provide for expression of the *K+Hnov* gene or variants thereof
in cells or tissues where it is not normally expressed or at abnormal times of
development.

25 DNA constructs for homologous recombination will comprise at least a
portion of the *K+Hnov* gene with the desired genetic modification, and will include
regions of homology to the target locus. DNA constructs for random integration
need not include regions of homology to mediate recombination. Conveniently,
markers for positive and negative selection are included. Methods for generating
30 cells having targeted gene modifications through homologous recombination are

known in the art. For various techniques for transfecting mammalian cells, see Kown *et al.* (1990) Methods in Enzymology **185**:527-537.

For embryonic stem (ES) cells, an ES cell line may be employed, or embryonic cells may be obtained freshly from a host, e.g. mouse, rat, guinea pig, etc. Such cells are grown on an appropriate fibroblast-feeder layer or grown in the presence of leukemia inhibiting factor (LIF). When ES or embryonic cells have been transformed, they may be used to produce transgenic animals. After transformation, the cells are plated onto a feeder layer in an appropriate medium. Cells containing the construct may be detected by employing a selective medium. After sufficient time for colonies to grow, they are picked and analyzed for the occurrence of homologous recombination or integration of the construct. Those colonies that are positive may then be used for embryo manipulation and blastocyst injection. Blastocysts are obtained from 4 to 6 week old superovulated females. The ES cells are trypsinized, and the modified cells are injected into the blastocoel of the blastocyst. After injection, the blastocysts are returned to each uterine horn of pseudopregnant females. Females are then allowed to go to term and the resulting offspring screened for the construct. By providing for a different phenotype of the blastocyst and the genetically modified cells, chimeric progeny can be readily detected.

The chimeric animals are screened for the presence of the modified gene and males and females having the modification are mated to produce homozygous progeny. If the gene alterations cause lethality at some point in development, tissues or organs can be maintained as allogeneic or congenic grafts or transplants, or in *in vitro* culture. The transgenic animals may be any non-human mammal, such as laboratory animals, domestic animals, etc. The transgenic animals may be used in functional studies, drug screening, etc., e.g. to determine the effect of a candidate drug on Ras or related gene activation, oncogenesis, etc.

TESTING OF K⁺HNOV FUNCTION and RESPONSES

Potassium channels such as K⁺Hnov polypeptides are involved in multiple biologically important processes. Pharmacological agents designed to affect only specific channel subtypes are of particular interest. Presently available
5 compounds tend to be non-specific and elicit both positive and negative responses, thereby reducing clinical efficacy.

The subject polypeptides may be used in *in vitro* and *in vivo* models to test the specificity of novel compounds, and of analogs and derivatives of compounds known to act on potassium channels. Numerous pharmacological agents have
10 profound effects on K⁺ channel activity. As examples, Sotalol (BETAPACE) is a class III antiarrhythmic drug that prolongs cardiac action potentials by inhibiting delayed rectifier K⁺ channels. Sulfonylurea drugs, such as Glipizide (GLUCOTROL) and Tolazamide (TOLAMIDE) function as antidiabetic drugs by blocking ATP-sensitive K⁺ channels present in pancreatic islet cells, thereby
15 regulating insulin secretion. Diazoxide (HYPERSTAT IV) is an antihypertensive drug that activates ATP-sensitive K⁺ channels, resulting in the relaxation of vascular smooth muscle. There are several other examples of drugs that have antidiabetic, antihypertensive, or antiarrhythmic activities. A number of drugs that activate K⁺ channels that have been proposed as coronary vasodilators for the
20 treatment of both vasospastic and chronic stable angina.

The availability of multiple K⁺ channel subunits allows *in vitro* reconstruction of functional channels, which may comprise different alpha and beta subunits. The individual components may be modified by sequence deletion, substitution, etc. to determine the functional role of specific domains.

25 Drug screening may be performed using an *in vitro* model, a genetically altered cell or animal, or purified K⁺Hnov protein, either as monomers, homomultimers or heteromultimers. One can identify ligands or substrates that bind to, modulate or mimic the action of K⁺Hnov. Drug screening identifies agents that provide a replacement for K⁺Hnov function in abnormal cells. Of
30 particular interest are screening assays for agents that have a low toxicity for human cells. A wide variety of assays may be used for this purpose, including

monitoring cellular excitation and conductance, labeled *in vitro* protein-prot in binding assays, electrophoretic mobility shift assays, immunoassays for protein binding, and the like. The purified protein may also be used for determination of three-dimensional crystal structure, which can be used for modeling
5 intermolecular interactions.

The term "agent" as used herein describes any molecule, e.g. protein or pharmaceutical, with the capability of altering or mimicking the physiological function of *K+Hnov* polypeptide. Generally a plurality of assay mixtures are run in parallel with different agent concentrations to obtain a differential response to the
10 various concentrations. Typically, one of these concentrations serves as a negative control, *i.e.* at zero concentration or below the level of detection.

Candidate agents encompass numerous chemical classes, though typically they are organic molecules, preferably small organic compounds having a molecular weight of more than 50 and less than about 2,500 daltons. Candidate
15 agents comprise functional groups necessary for structural interaction with proteins, particularly hydrogen bonding, and typically include at least an amine, carbonyl, hydroxyl or carboxyl group, preferably at least two of the functional chemical groups. The candidate agents often comprise cyclical carbon or heterocyclic structures and/or aromatic or polyaromatic structures substituted with
20 one or more of the above functional groups. Candidate agents are also found among biomolecules including peptides, saccharides, fatty acids, steroids, purines, pyrimidines, derivatives, structural analogs or combinations thereof.

Candidate agents are obtained from a wide variety of sources including libraries of synthetic or natural compounds. For example, numerous means are
25 available for random and directed synthesis of a wide variety of organic compounds and biomolecules, including expression of randomized oligonucleotides and oligopeptides. Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant and animal extracts are available or readily produced. Additionally, natural or synthetically produced libraries and compounds
30 are readily modified through conventional chemical, physical and biochemical means, and may be used to produce combinatorial libraries. Known

pharmacological agents may be subjected to directed or random chemical modifications, such as acylation, alkylation, esterification, amidification, *etc.* to produce structural analogs.

Where the screening assay is a binding assay, one or more of the
5 molecules may be joined to a label, where the label can directly or indirectly provide a detectable signal. Various labels include radioisotopes, fluorescers, chemilumescers, enzymes, specific binding molecules, particles, *e.g.* magnetic particles, and the like. Specific binding molecules include pairs, such as biotin and streptavidin, digoxin and antidigoxin *etc.* For the specific binding members,
10 the complementary member would normally be labeled with a molecule that provides for detection, in accordance with known procedures.

A variety of other reagents may be included in the screening assay. These include reagents like salts, neutral proteins, *e.g.* albumin, detergents, *etc.* that are used to facilitate optimal protein-protein binding and/or reduce non-specific or
15 background interactions. Reagents that improve the efficiency of the assay, such as protease inhibitors, nuclease inhibitors, anti-microbial agents, *etc.* may be used. The mixture of components are added in any order that provides for the requisite binding. Incubations are performed at any suitable temperature, typically between 4 and 40°C. Incubation periods are selected for optimum
20 activity, but may also be optimized to facilitate rapid high-throughput screening. Typically between 0.1 and 1 hours will be sufficient.

The compounds having the desired pharmacological activity may be administered in a physiologically acceptable carrier to a host in a variety of ways, orally, topically, parenterally *e.g.* subcutaneously, intraperitoneally, by viral
25 infection, intravascularly, *etc.* Depending upon the manner of introduction, the compounds may be formulated in a variety of ways. The concentration of therapeutically active compound in the formulation may vary from about 0.1-100 wt.%. The pharmaceutical compositions can be prepared in various forms, such as granules, tablets, pills, suppositories, capsules, suspensions,
30 salves, lotions and the like. Pharmaceutical grade organic or inorganic carriers and/or diluents suitable for oral and topical use can be used to make up

compositions containing the therapeutically-active compounds. Diluents known to the art include aqueous media, vegetable and animal oils and fats. Stabilizing agents, wetting and emulsifying agents, salts for varying the osmotic pressure or buffers for securing an adequate pH value, and skin penetration enhancers can
5 be used as auxiliary agents.

It is to be understood that this invention is not limited to the particular methodology, protocols, cell lines, animal species or genera, and reagents described, as such may vary. It is also to be understood that the terminology
10 used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

As used herein the singular forms "a", "and", and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example,
15 reference to "a cell" includes a plurality of such cells and reference to "the cell" includes reference to one or more cells and equivalents thereof known to those skilled in the art, and so forth. All technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this invention belongs unless clearly indicated otherwise.

20 It must be noted that as used herein and in the appended claims, the singular forms "a", "and", and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a complex" includes a plurality of such complexes and reference to "the formulation" includes reference to one or more formulations and equivalents thereof known to those skilled in the
25 art, and so forth.

All publications mentioned herein are incorporated herein by reference for the purpose of describing and disclosing, for example, the methods and methodologies that are described in the publications which might be used in connection with the presently described invention. The publications discussed
30 above and throughout the text are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an

admission that the inventors are not entitled to antedate such disclosure by virtue of prior invention.

EXPERIMENTAL

5 The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the subject invention, and are not intended to limit the scope of what is regarded as the invention. Efforts have been made to ensure accuracy with respect to the numbers used (e.g. amounts, temperature, concentrations, etc.) but some
10 experimental errors and deviations should be allowed for. Unless otherwise indicated, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees centigrade; and pressure is at or near atmospheric.

15 Methods

Two different types of sequence searches were performed. The first centered on the most highly conserved region of the K⁺ channel family, the pore domain. The pore is composed of 15-17 amino acids and can be divided into subfamilies based on the number of transmembrane segments present in the
20 channel. Eleven variant peptide sequences corresponding to the pore domain were used in TBLASTN searches against the EST division of Genbank. Significant matches were identified, and classified into 2 categories: identical to known human K⁺ channels and related to known K⁺ channels. The pore sequences are shown in Table 2.

TABLE 2

SEQ ID NO	Genbank #	
49	L02751	TGGTGGGCTGTGGTGACCATGACAACTGTGGGCTATGGGACATG
50	M80451	TGGTGGGCAGTGGTCACCATGACCACTGTGGGCTACGGGGACATG
51	L02752	TGGTGGGCAGTCGTCTCCATGACAACTGTAGGCTATGGAGACATG
52	M55515	TGGTGGGCAGTGGTAACCATGACAACAGTGGGTTACGGCGATATG
53	Z11585	TGGTGGGCTGTGGTCACCATGACGACCCCTGGGCTATGGAGACATG
54	U40890	TGGTGGGGGTGGTCACAGTCACCACTACCACTCGGCTATGGGACAAG
55	I28843	TGGTGGGCAGTGGTCACCATGACCACGGTTGGCTATGGGACATG
56	M88747	TGGTGGGCCGTGGTCACCATGACGACCCCTGGGCTATGGAGACATG
57	M84876	TGGTGGGCTGTGGTCACCATGACGACACTGGGCTACGGAGACATG
58	M55514	TGGTGGGCTGTGGTGACCATGACAACTGTGGGCTATGGGGACATG
59	X83582	TTCTGTTCTCATTGAGACCGAACAACCAATGGGTATGGCTTCCG
60	S78884	TTTTTATTCTCAATAGAGACAGAAACCACTTGGTTATGGCTACCG
61	U22413	TTCTCTCTCTCCATTGAGACCCAGACAACCACTAGGCTATGGTTTCAG
62	U24058	TTCTGTTCTCGGTGGAGACGACGACGACCATCGGCTATGGGTTCCG
63	U52155	TTCTCTCTCTCCCTTGAAATCCCAACCACTTGGCTATGGCTTCCG
64	D87291	TTCTCTCTCTCCCTGGAATCCAGACAACCACTTGGCTATGGAGTCCG
65	D50582	TTCTCTCTCTCCATTGAGGTCCAAAGTGACTATTGGCTTTGGGGGGCG
66	D50315	TTCTCTCTCTCCATTGAAGTTCAAGTTACCACTTGGGTTTGGAGGGAG
67	U04270	GGGCTCTACTTCACCTTCAGCAGCCCTCACCAGTGTGGGCTTCGGCAAC

The unique pore p ptid s sequences are shown in Table 3.

TABLE 3

SEQ ID NO	Amino acid sequence
68	WWAWVSMTTVGYGDM
69	WWAWVTMTTLGYGDM
70	WWGWTVTTIGYGDK
71	WWAWVTMTTVGYGDM
72	FLFSIEVQVTIGFGG
73	FLFSLESQTTIGYGV
74	FLFSIETETTIGYGY
75	FLFSIETQTTIGYGF
76	FLFSVETQTTIGYGF
77	FLFSLESQTTIGYGF
78	FLFSIETETTIGYGF
79	ALYFTFSSLTSVGFGN

- 5 The second set of experiments was based on a complex, reiterative process. Annotated protein and DNA sequences were obtained from GenBank for all known K⁺ channels from all species. The TBLASTN and BLASTN programs were used to identify homologous ESTs, which were then analyzed using the BLASTX and BLASTN algorithms to identify ESTs which were related to K⁺ channels yet not identical to any
- 10 known human K⁺ channel gene.

Novel human K⁺ channels were defined as those that had clear homology to known K⁺ channels from any species and were not present as identities or near identities to any human-derived sequences in any division of Genbank.

- 15 *Isolation of full length cDNA sequence.* EST clones were picked from the IMAGE consortium cDNA library and end-sequenced with vector primers. Gap closure was achieved either by primer walking or transposon sequencing. GeneTrapper (Life

Technologies) was used to isolate larger cDNA clones according to the provided protocol. RACE was used to extend the sequences as necessary using standard protocols.

Sequences were assembled in Sequencher (Gene Codes). The presence of open reading frames was assessed as well as potential start codons. Potential polymorphisms were detected as sequence variants between multiple independent clones. Sequence homologies were detected using the BLAST algorithms.

The completed gene sequences and predicted amino acid sequences are provided as SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21-24, 26 and 28-29. Polymorphisms, chromosome locations and family assignments are shown in Table 1.

ESTs that had top human hits with >95% identity over 100 amino acids were discarded. This was based upon the inventors' experience that these sequences were usually identical to the starting probe sequences, with the differences due to sequence error. The remaining BLASTN and BLASTX outputs for each EST were examined manually, i.e., ESTs were removed from the analysis if the inventors determined that the variation from the known related probe sequence was a result of poor database sequence. Poor database sequence was usually identified as a number of 'N' nucleotides in the database sequence for a BLASTN search and as a base deletion or insertion in the database sequence, resulting in a peptide frameshift, for a BLASTX output. ESTs for which the highest scoring match was to non-related sequences were also discarded at this stage. The EST sequences that correspond to each clone are shown in Table 4.

Table 4

Genbank Accession#	K+Hnov	clone ID	Trace	IMAGE Plate Coordinates	Read 5'/3'
N39619	K+Hnov2	277113	yy51h05.s1	611p10	3'
N46767	K+Hnov2	277113	yy51h05.r1	611p10	5'
R19352	K+Hnov11	33144	yg24f12.r1	155o24	5'
R44628	K+Hnov11	33144	yg24f12.s1	155o24	3'

R35526	K+Hnov14	37299	yg64e08.r1	165o15	5'
R73353	K+Hnov14	157854	yl10e04.r1	251g07	5'
AA397616	K+Hnov14	728558	zt79c08.r1	1787j15	5'
AA286692	K+Hnov28	700757	zs48h03.r1	1715d6	5'
AA150494	K+Hnov42	491748	zl08e07.s1	1170o13	3'
AA156697	K+Hnov42	491748	zl08e07.r1	1170o13	5'
AA191752	K+Hnov42	626699	zp82d06.r1	1522f12	5'
AA216446	K+Hnov42	626699	zp82d06.s1	1522f12	3'
AA430591	K+Hnov42	773611	zw51f10.r1	1904o20	5'
AA236930	K+Hnov44	683888	zs01a05.s1	1671e9	3'
AA236968	K+Hnov44	683888	zs01a05.r1	1671e9	5'

EXAMPLE 2: CHROMOSOMAL LOCALIZATION

Two primers were designed in the 3'-untranslated regions of each gene sequence to amplify a product across the Stanford G3 radiation hybrid map, or the Whitehead GB4 panel. The PCR data were submitted for automatic two-point analysis. Mapping data were correlated with cytoband information and comparisons with the OMIM human gene map data base were made. The following primers were made:

- 10 K+Hnov1 on GB4
(SEQ ID NO:31) F: 5' TATCCACATCAATGGACAAAGC 3'
(SEQ ID NO:32) R: 5' TGCATAACTGGCTGGGTGTA 3'
Results: 1.71 cR from D2S331, Cytogenetic location of 2q37
- 15 K+Hnov2 on G3
F: 5' GTCAGGTGACCGAGTTCA 3'
R: 5' GCTCCATCTCCAGATTCTTC 3'
Results: 0.0 cR from SHGC-1320, Cytogenetic location of 11q12
- 20 K+Hnov6 on GB4
(SEQ ID NO:33) F: 5' TGACATCACTGGATGAACTTGA 3'
(SEQ ID NO:34) R: 5' TGCCTGCAAAGTTTGAACAT 3'
Results: 5.23 cR from WI-5509, Cytogenetic location of 2p23
- 25 K+Hnov9 on GB4
(SEQ ID NO:35) F: 5' TGACATCACTGGATGAACTTGA 3'
(SEQ ID NO:36) R: 5' TGCCTGCAAAGTTTGAACAT 3'

Results: 1.21 cR from AFM200VC7, Cytogenetic location of 8q23

K+Hnov11 on GB4

(SEQ ID NO:37) F: 5' ACCTGGTGGTATGGAAGCAT 3'

5 (SEQ ID NO:38) R: 5' TTTCTCCTGGCCTCTACCC 3'

Results: 2.43 cR from WI-6756, Cytogenetic location of 8q23

K+Hnov12 on G3

(SEQ ID NO:39) F: 5' TCCCTCTTGGGTGACCTTC 3'

10 (SEQ ID NO:40) R: 5' ATCTTTGTCAGCCACCAGCT 3'

Results: 7.45 cR from SHGC-32925, Cytogenetic location of Xp21

K+Hnov14 on GB4

(SEQ ID NO:41) F: 5' AGGTGTGCTGCCATCTGCTGTTCG3'

15 (SEQ ID NO:42) R: 5' AGCCTATCCTCTCTGAGAGTCAGG

Results: 7.69 cR from WI-7107, Cytogenetic location of 12q14

K+Hnov28 on GB4

(SEQ ID NO:43) F: 5' AAGCAGAGTACTCATGATGCC 3'

20 (SEQ ID NO:44) R: 5' TCTGGTAGACAGTACAGTGG 3'

Results: 35.38 cR from WI-9695, Cytogenetic location of 3q29

K+Hnov42 on G3

(SEQ ID NO:45) F: 5' CATTTGGCTGGTCCAAGATG 3'

25 (SEQ ID NO:46) R: 5' AGTCATTGGTAGGGAGGTAC 3'

Results: 7.45 cR from SHGC-32925, Cytogenetic location of Xp21

K+Hnov44 on G3

(SEQ ID NO:47) F: 5' CATGCTTCTACAGTCCAGCC 3'

30 (SEQ ID NO:48) R: 5' GGTCCTCAGTTGCAGAAATC 3'

Results: 7.45 cR from SHGC-32925, Cytogenetic location of Xp21

Map positions for K+Hnov15 and K+Hnov27 were obtained from public databases.

K+Hnov2 and K+Hnov4 have not been mapped.

35

EXAMPLE 3: EXPRESSION ANALYSIS

RT-PCR was utilized to characterize the expression pattern of the novel ion channels. This approach used RNA from 30 different tissues to generate first strand cDNA. Total RNA was purchased (Clontech, Invitrogen) and used to synthesize first strand cDNA using M-MLV reverse transcriptase and the supplied buffer (Gibco-BRL).

40 The 20 µl reaction contained 5 µg total RNA, 100 ng of random primers, 10 mM DTT,

0.5 mM each dNTP, and an RNase inhibitor (Gibco-BRL). Identical reactions were set up without reverse transcriptase to control for DNA contamination in the RNA samples. The synthesis reaction proceeded for 1 hour at 37°C followed by 10 minutes at 95°C. These cDNAs, along with control cDNA synthesis reactions without reverse transcriptase, were diluted 1:5 and 2 µl of each sample were arrayed into 96-well trays, dried, and resuspended in PCR buffer prior to PCR amplification. The cDNAs were tested with primers with defined expression patterns to verify the presence of amplifiable cDNA from each tissue. Gene-specific primers were used to amplify the cDNAs in 20 µl PCR reactions with standard conditions, 2.5 mM MgCl₂, Taq Gold, and an appropriate annealing temperature.

This approach provides for relatively high-throughput analysis of gene expression in a large set of tissues in a cost-efficient manner and provides qualitative analysis of gene expression only. Modifications can be employed, such as the use of internal control primers, limited cycling parameters, and dilution series to convert this to a quantitative experiment.

Table 3

[illegible]

A "+" indicates expression in the tissue, a "-" indicates no expression, and blank square indicates no data for that sample.

K+Hnov49 on Whitehead GB4 RH mapping panel:

Primer 1 (SEQ ID NO:5): 5' - CATAGCCATAGGTGAGGACT - 3'

Primer 2: (SEQ ID NO:6) 5' - GAGAGGAAAACAGTCTGGGC - 3'

- 5 Results: Cytogenetic location 1q41, 4.6cR from framework marker D1S217

K+Hnov59 on Whitehead GB4 RH mapping panel

Primer 1 (SEQ ID NO:7): 5' - GGACATCGAACTAAGACCTG - 3'

Primer 2 (SEQ ID NO:8): 5' - TCCCATGCCATTCAGATCTG - 3'

- 10 Results: Cytogenetic location 19q13.2, 8.34cR from framework marker D19S425

EXPRESSION ANALYSIS OF K+HNOV49

- 15 A probe was created from a fragment corresponding to nucleotides 50 to 1284 of SEQ ID NO:83 (K+Hnov49) and purified DNA fragment was labeled with [³²P]dCTP (Amersham) by the random primer method. Adult human Multiple Tissue Northern (MTM™) Blots (Clontech) were hybridized with the [³²P]-labeled fragment in ExpressHyb™ solution (Clontech) for four hours, washed to a final stringency of 0.1xSSC, 0.1% SDS at 65°C and subjected to autoradiography for 24 hours.

- 20 Analysis revealed that K+Hnov49 is expressed as an approximately 4.2kb mRNA. Expression levels of K+Hnov49 are high in brain and liver and low in kidney tissues. No mRNA was detectable on these Northern blots for heart, skeletal muscle, colon, thymus, spleen, small intestine, placenta, lung or peripheral blood leukocytes indicating either a very low level of expression or that
25 it is not expressed in these tissues. Expression analysis was also carried out by RT-PCR across an extended series of tissues. The results of these analyses are shown in Table 4. Primer pairs used for amplification of K+Hnov49 and 59 are the same as those used for RH mapping as indicated above.

Table 4

基	基	Adipose	Adrenal Gland	Bladder	Brain	Cerebellum	Cervix	Colon	Esophagus	Fetal Brain	Fetal Liver	Heart	HeLa Cell	Kidney	Liver	Lung	Mammary Gland	Pancreas	Placenta	Prostate	Rectum	Salivary Gland	Skeletal Muscle	Skin	Small Intestine	Spleen	Stomach	Testis	Thymus	Trachea	Uterus
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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WHAT IS CLAIMED IS:

1. An isolated nucleic acid encoding a mammalian K+Hnov protein.
2. An isolated nucleic acid according to Claim 1, wherein said K+Hnov
5 protein has the amino acid sequence of SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 25, 27, 30, 81 or 83.
3. An isolated nucleic acid according to Claim 1, wherein said K+Hnov
10 protein has an amino acid sequence that is substantially identical to the amino acid sequence of SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 25, 27, 30, 81 or 83.
4. An isolated nucleic acid according to Claim 1 wherein the nucleotide
15 sequence of said nucleic acid is SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 22, 23, 24, 26, 28, 29, 80 or 82.
5. An isolated nucleic acid that hybridizes under stringent conditions to a nucleic acid sequence of claim 4.
- 20 6. An expression cassette comprising a transcriptional initiation region functional in an expression host, a nucleic acid having a sequence of the isolated nucleic acid according to Claim 1 under the transcriptional regulation of said transcriptional initiation region, and a transcriptional termination region functional in said expression host.
- 25 7. A cell comprising an expression cassette according to Claim 6 as part of an extrachromosomal element or integrated into the genome of a host cell as a result of introduction of said expression cassette into said host cell, and the cellular progeny of said host cell.
- 30

8. A method for producing mammalian K+Hnov protein, said method comprising:

growing a cell according to Claim 7, whereby said mammalian K+Hnov protein is expressed; and

5 isolating said K+Hnov protein free of other proteins.

9. A purified polypeptide composition comprising at least 50 weight % of the protein present as a K+Hnov protein or a fragment thereof.

10 10. A monoclonal antibody binding specifically to a K+Hnov protein.

11. A non-human transgenic animal model for K+Hnov gene function wherein said transgenic animal comprises an introduced alteration in a K+Hnov gene.

15

12. The animal model of claim 11, wherein said animal is heterozygous for said introduced alteration.

13. The animal model of claim 12, wherein said animal is homozygous
20 for said introduced alteration.

14. The animal model of claim 12, wherein said introduced alteration is a knockout of endogenous K+Hnov gene expression.

SEQUENCE LISTING

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Buckler, Alan

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gaa aca cat gaa gct ttc aat att gtt aaa aac aag aca gaa cca gtc Glu Thr His Glu Ala Phe Asn Ile Val Lys Asn Lys Thr Glu Pro Val 215 220 225	788
atc aat ggc aca agt gtt gtt cta cag tat gaa att gaa acg gat cct Ile Asn Gly Thr Ser Val Val Leu Gln Tyr Glu Ile Glu Thr Asp Pro 230 235 240	836
gcc ttg acg tat gta gaa gga gtg tgt gtg gtg tgg ttt act ttt gaa Ala Leu Thr Tyr Val Glu Gly Val Cys Val Val Trp Phe Thr Phe Glu 245 250 255 260	884
ttt tta gtc cgt att gtt ttt tca ccc aat aaa ctt gaa ttc atc aaa Phe Leu Val Arg Ile Val Phe Ser Pro Asn Lys Leu Glu Phe Ile Lys 265 270 275	932
aat ctc ttg aat atc att gac ttt gtg gcc atc cta cct ttc tac tta Asn Leu Leu Asn Ile Ile Asp Phe Val Ala Ile Leu Pro Phe Tyr Leu 280 285 290	980
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Glu Val Gly Leu Ser Gly Leu Ser Ser Lys Ala Ala Lys Asp Val Leu	
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Gly Phe Leu Arg Val Val Arg Phe Val Arg Ile Leu Arg Ile Phe Lys	
310 315 320	
ctc acc cgc cat ttt gta ggt ctg agg gtg ctt gga cat act ctt cga	1124
Leu Thr Arg His Phe Val Gly Leu Arg Val Leu Gly His Thr Leu Arg	
325 330 335 340	
gct agt act aat gaa ttt ttg ctg ctg ata att ttc ctg gct cta gga	1172
Ala Ser Thr Asn Glu Phe Leu Leu Leu Ile Ile Phe Leu Ala Leu Gly	
345 350 355	
gtt ttg ata ttt gct acc atg atc tac tat gcc gag aga gtg gga gct	1220
Val Leu Ile Phe Ala Thr Met Ile Tyr Tyr Ala Glu Arg Val Gly Ala	
360 365 370	
caa cct aac gac cct tca gct agt gag cac aca cag ttc aaa aac att	1268
Gln Pro Asn Asp Pro Ser Ala Ser Glu His Thr Gln Phe Lys Asn Ile	
375 380 385	
ccc att ggg ttc tgg tgg gct gta gtg acc atg act acc ctg ggt tat	1316
Pro Ile Gly Phe Trp Trp Ala Val Val Thr Met Thr Thr Leu Gly Tyr	
390 395 400	
ggg gat atg tac ccc caa aca tgg tca ggc atg ctg gtg gga gcc ctg	1364
Gly Asp Met Tyr Pro Gln Thr Trp Ser Gly Met Leu Val Gly Ala Leu	
405 410 415 420	
tgt gct ctg gct gga gtg ctg aca ata gcc atg cca gtg cct gtc att	1412
Cys Ala Leu Ala Gly Val Leu Thr Ile Ala Met Pro Val Pro Val Ile	
425 430 435	
gtc aat aat ttt gga atg tac tac tcc ttg gca atg gca aag cag aaa	1460
Val Asn Asn Phe Gly Met Tyr Tyr Ser Leu Ala Met Ala Lys Gln Lys	
440 445 450	
ctt cca agg aaa aga aag aag cac atc cct cct gct cct cag gca agc	1508
Leu Pro Arg Lys Arg Lys Lys His Ile Pro Pro Ala Pro Gln Ala Ser	
455 460 465	
tca cct act ttt tgc aag aca gaa tta aat atg gcc tgc aat agt aca	1556
Ser Pro Thr Phe Cys Lys Thr Glu Leu Asn Met Ala Cys Asn Ser Thr	
470 475 480	
cag agt gac aca tgt ctg ggc aaa gac aat cga ctt ctg gaa cat aac	1604
Gln Ser Asp Thr Cys Leu Gly Lys Asp Asn Arg Leu Leu Glu His Asn	
485 490 495 500	
aga tca gtg tta tca ggt gac gac agt aca gga agt gag ccg cca cta	1652
Arg Ser Val Leu Ser Gly Asp Asp Ser Thr Gly Ser Glu Pro Pro Leu	
505 510 515	
tca ccc cca gaa agg ctc ccc atc aga cgc tct agt acc aga gac aaa	1700
Ser Pro Pro Glu Arg Leu Pro Ile Arg Arg Ser Ser Thr Arg Asp Lys	
520 525 530	
aac aga aga ggg gaa aca tgt ttc cta ctg acg aca ggt gat tac acg	1748
Asn Arg Arg Gly Glu Thr Cys Phe Leu Leu Thr Thr Gly Asp Tyr Thr	

535	540	545	
tgt gct tct gat gga ggg atc agg aaa gga tat gaa aaa tcc cga agc			1796
Cys Ala Ser Asp Gly Gly Ile Arg Lys Gly Tyr Glu Lys Ser Arg Ser			
550	555	560	
tta aac aac ata gcg ggc ttg gca ggc aat gct ctg agg ctc tct cca			1844
Leu Asn Asn Ile Ala Gly Leu Ala Gly Asn Ala Leu Arg Leu Ser Pro			
565	570	575	580
gta aca tca ccc tac aac tct cct tgt cct ctg agg cgc tct cga tct			1892
Val Thr Ser Pro Tyr Asn Ser Pro Cys Pro Leu Arg Arg Ser Arg Ser			
585	590	595	
ccc atc cca tct atc t cgtaaaccaa accctcgtg			1927
Pro Ile Pro Ser Ile			
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Arg Leu Ala Trp Leu Ala Asp Pro Asp Gly Gly Gly Arg Pro Glu Thr			
35	40	45	
Asp Gly Gly Gly Val Gly Ser Ser Gly Ser Ser Gly Gly Gly Gly Cys			
50	55	60	
Glu Phe Phe Phe Asp Arg His Pro Gly Val Phe Ala Tyr Val Leu Asn			
65	70	75	80
Tyr Tyr Arg Thr Gly Lys Leu His Cys Pro Ala Asp Val Cys Gly Pro			
85	90	95	
Leu Phe Glu Glu Glu Leu Ala Phe Trp Gly Ile Asp Glu Thr Asp Val			
100	105	110	
Glu Pro Cys Cys Trp Met Thr Tyr Arg Gln His Arg Asp Ala Glu Glu			
115	120	125	
Ala Leu Asp Ile Phe Glu Thr Pro Asp Leu Ile Gly Gly Asp Pro Gly			
130	135	140	
Asp Asp Glu Asp Leu Ala Ala Lys Arg Leu Gly Ile Glu Asp Ala Ala			
145	150	155	160
Gly Leu Gly Gly Pro Asp Gly Lys Ser Gly Arg Trp Arg Arg Leu Gln			
165	170	175	
Pro Arg Met Trp Ala Leu Phe Glu Asp Pro Tyr Ser Ser Arg Ala Ala			
180	185	190	
Arg Phe Ile Ala Phe Ala Ser Leu Phe Phe Ile Leu Val Ser Ile Thr			
195	200	205	
Thr Phe Cys Leu Glu Thr His Glu Ala Phe Asn Ile Val Lys Asn Lys			
210	215	220	
Thr Glu Pro Val Ile Asn Gly Thr Ser Val Val Leu Gln Tyr Glu Ile			
225	230	235	240
Glu Thr Asp Pro Ala Leu Thr Tyr Val Glu Gly Val Cys Val Val Trp			
245	250	255	
Phe Thr Phe Glu Phe Leu Val Arg Ile Val Phe Ser Pro Asn Lys Leu			
260	265	270	
Glu Phe Ile Lys Asn Leu Leu Asn Ile Ile Asp Phe Val Ala Ile Leu			
275	280	285	

Pro Phe Tyr Leu Glu Val Gly Leu Ser Gly Leu Ser Ser Lys Ala Ala
 290 295 300
 Lys Asp Val Leu Gly Phe Leu Arg Val Val Arg Phe Val Arg Ile Leu
 305 310 315 320
 Arg Ile Phe Lys Leu Thr Arg His Phe Val Gly Leu Arg Val Leu Gly
 325 330 335
 His Thr Leu Arg Ala Ser Thr Asn Glu Phe Leu Leu Leu Ile Ile Phe
 340 345 350
 Leu Ala Leu Gly Val Leu Ile Phe Ala Thr Met Ile Tyr Tyr Ala Glu
 355 360 365
 Arg Val Gly Ala Gln Pro Asn Asp Pro Ser Ala Ser Glu His Thr Gln
 370 375 380
 Phe Lys Asn Ile Pro Ile Gly Phe Trp Trp Ala Val Val Thr Met Thr
 385 390 395 400
 Thr Leu Gly Tyr Gly Asp Met Tyr Pro Gln Thr Trp Ser Gly Met Leu
 405 410 415
 Val Gly Ala Leu Cys Ala Leu Ala Gly Val Leu Thr Ile Ala Met Pro
 420 425 430
 Val Pro Val Ile Val Asn Asn Phe Gly Met Tyr Tyr Ser Leu Ala Met
 435 440 445
 Ala Lys Gln Lys Leu Pro Arg Lys Arg Lys Lys His Ile Pro Pro Ala
 450 455 460
 Pro Gln Ala Ser Ser Pro Thr Phe Cys Lys Thr Glu Leu Asn Met Ala
 465 470 475 480
 Cys Asn Ser Thr Gln Ser Asp Thr Cys Leu Gly Lys Asp Asn Arg Leu
 485 490 495
 Leu Glu His Asn Arg Ser Val Leu Ser Gly Asp Asp Ser Thr Gly Ser
 500 505 510
 Glu Pro Pro Leu Ser Pro Pro Glu Arg Leu Pro Ile Arg Arg Ser Ser
 515 520 525
 Thr Arg Asp Lys Asn Arg Arg Gly Glu Thr Cys Phe Leu Leu Thr Thr
 530 535 540
 Gly Asp Tyr Thr Cys Ala Ser Asp Gly Gly Ile Arg Lys Gly Tyr Glu
 545 550 555 560
 Lys Ser Arg Ser Leu Asn Asn Ile Ala Gly Leu Ala Gly Asn Ala Leu
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 gagaacagga ttcttccctt ctttttggcc accaaatgcc tatgtgcacc acacattcca 180
 gtgtgctgag aagggcagag cttcttgat gatgatggac gtcccaccgg gcaggatgaa 240
 ggcagagcgt gtggcatctc cactcaagg gtgcagcctg atcttctct tctcccttgc 300
 cagccagcac tctgccttct gtatccacc atg gtg ttt ggt gag ttt ttc cat 353
 Met Val Phe Gly Glu Phe Phe His
 1 5

cgc cct gga caa gac gag gaa ctt gtc aac ctg aat gtg ggg ggc ttt	401
Arg Pro Gly Gln Asp Glu Glu Leu Val Asn Leu Asn Val Gly Gly Phe	
10 15 20	
aag cag tct gtt gac caa agc acc ctc ctg cgg ttt cct cac acc aga	449
Lys Gln Ser Val Asp Gln Ser Thr Leu Leu Arg Phe Pro His Thr Arg	
25 30 35 40	
ctg ggg aag ctg ctt act tgc cat tct gaa gag gcc att ctg gag ctg	497
Leu Gly Lys Leu Leu Thr Cys His Ser Glu Glu Ala Ile Leu Glu Leu	
45 50 55	
tgt gat gat tac agt gtg gcc gat aag gaa tac tac ttt gat cgg aat	545
Cys Asp Asp Tyr Ser Val Ala Asp Lys Glu Tyr Tyr Phe Asp Arg Asn	
60 65 70	
ccc tcc ttg ttc aga tat gtt ttg aat ttt tat tac acg ggg aag ctg	593
Pro Ser Leu Phe Arg Tyr Val Leu Asn Phe Tyr Tyr Thr Gly Lys Leu	
75 80 85	
cat gtc atg gag gag ctg tgc gta ttc tca ttc tgc cag gag atc gag	641
His Val Met Glu Glu Leu Cys Val Phe Ser Phe Cys Gln Glu Ile Glu	
90 95 100	
tac tgg ggc atc aac gag ctc ttc att gat tct tgc tgc agc aat cgc	689
Tyr Trp Gly Ile Asn Glu Leu Phe Ile Asp Ser Cys Cys Ser Asn Arg	
105 110 115 120	
tac cag gaa cgc aag gag gaa aac cac gag aag gac tgg gac cag aaa	737
Tyr Gln Glu Arg Lys Glu Glu Asn His Glu Lys Asp Trp Asp Gln Lys	
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Ser His Asp Val Ser Thr Asp Ser Ser Phe Glu Glu Ser Ser Leu Phe	
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gag aaa gag ctg gag aag ttt gac aca ctg cga ttt ggt cag ctc cgg	833
Glu Lys Glu Leu Glu Lys Phe Asp Thr Leu Arg Phe Gly Gln Leu Arg	
155 160 165	
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Lys Lys Ile Trp Ile Arg Met Glu Asn Pro Ala Tyr Cys Leu Ser Ala	
170 175 180	
aag ctt atc gct atc tcc tcc ttg agc gtg gtg ctg gcc tcc atc gtg	929
Lys Leu Ile Ala Ile Ser Ser Leu Ser Val Val Leu Ala Ser Ile Val	
185 190 195 200	
gcc atg tgc gtt cac agc atg tcg gag ttc cag aat gag gat gga gaa	977
Ala Met Cys Val His Ser Met Ser Glu Phe Gln Asn Glu Asp Gly Glu	
205 210 215	
gtg gat gat ccg gtg ctg gaa gga gtg gag atc gcg tgc att gcc tgg	1025
Val Asp Asp Pro Val Leu Glu Gly Val Glu Ile Ala Cys Ile Ala Trp	
220 225 230	
ttc acc ggg gag ctt gcc gtc cgg ctg gct gcc gct cct tgt caa aag	1073
Phe Thr Gly Glu Leu Ala Val Arg Leu Ala Ala Ala Pro Cys Gln Lys	
235 240 245	
aaa ttc tgg aaa aac cct ctg aac atc att gac ttt gtc tct att att	1121

Lys Phe Trp Lys Asn Pro Leu Asn Ile Ile Asp Phe Val Ser Ile Ile 250 255 260	
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gat att gag aac atg ggc aag gtg gtc cag atc cta cgg ctt atg agg Asp Ile Glu Asn Met Gly Lys Val Val Gln Ile Leu Arg Leu Met Arg 285 290 295	1217
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cta ggt gcc aca ctg aga cac agc tac cat gaa gtt ggg ctt ctg ctt Leu Gly Ala Thr Leu Arg His Ser Tyr His Glu Val Gly Leu Leu Leu 315 320 325	1313
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cac ccg gtc acc ttg gcg gga aag ctc atc gcc agc aca tgc atc atc His Pro Val Thr Leu Ala Gly Lys Leu Ile Ala Ser Thr Cys Ile Ile 380 385 390	1505
tgt ggc atc ttg gtg gtg gcc ctt ccc atc acc atc atc ttc aac aag Cys Gly Ile Leu Val Val Ala Leu Pro Ile Thr Ile Ile Phe Asn Lys 395 400 405	1553
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agt gag gat gca cca gag aag tgt cat gag cta cct tac ttt aac att Ser Glu Asp Ala Pro Glu Lys Cys His Glu Leu Pro Tyr Phe Asn Ile 425 430 435 440	1649
agg gat ata tat gca cag cgg atg cac gcc ttc att acc agt ctc tct Arg Asp Ile Tyr Ala Gln Arg Met His Ala Phe Ile Thr Ser Leu Ser 445 450 455	1697
tct gta ggc att gtg gtg agc gat cct gac tcc aca gat gct tca agc Ser Val Gly Ile Val Val Ser Asp Pro Asp Ser Thr Asp Ala Ser Ser 460 465 470	1745
att gaa gac aat gag gac att tgt aac acc acc tcc ttg gag aat tgc Ile Glu Asp Asn Glu Asp Ile Cys Asn Thr Thr Ser Leu Glu Asn Cys 475 480 485	1793
aca gca a aatgagcggg ggtgtttgtg cctgtttctc ttatcctttc ccaacattag Thr Ala	1850

490

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gttaacacag ctttataaac ctcagtgggt tcgttaaaat catttaattc tcagggtgta 1910
cctttcagcc atagttggac attcattgct gaattctgaa atgatagaat tgtctttatt 1970
tttctctgtg aggtcaatta aatgccttgt tctgaaattt attttttaca agagagagtt 2030
gtgatagagt ttggaatata agataaatgg tattgggtgg ggtttgtggc tacagcttat 2090
gcatcattct gtgtttgtca tttactcaca ttgagctaac tttaaattac tgacaagtag 2150
aatcaaaggt gcagctgact gagacgacat gcatgtaaga tccacaaaat gagacaatgc 2210
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Leu Leu Arg Phe Pro His Thr Arg Leu Gly Lys Leu Leu Thr Cys His
35      40      45
Ser Glu Glu Ala Ile Leu Glu Leu Cys Asp Asp Tyr Ser Val Ala Asp
50      55      60
Lys Glu Tyr Tyr Phe Asp Arg Asn Pro Ser Leu Phe Arg Tyr Val Leu
65      70      75      80
Asn Phe Tyr Tyr Thr Gly Lys Leu His Val Met Glu Glu Leu Cys Val
85      90      95
Phe Ser Phe Cys Gln Glu Ile Glu Tyr Trp Gly Ile Asn Glu Leu Phe
100     105     110
Ile Asp Ser Cys Cys Ser Asn Arg Tyr Gln Glu Arg Lys Glu Glu Asn
115     120     125
His Glu Lys Asp Trp Asp Gln Lys Ser His Asp Val Ser Thr Asp Ser
130     135     140
Ser Phe Glu Glu Ser Ser Leu Phe Glu Lys Glu Leu Glu Lys Phe Asp
145     150     155     160
Thr Leu Arg Phe Gly Gln Leu Arg Lys Lys Ile Trp Ile Arg Met Glu
165     170     175
Asn Pro Ala Tyr Cys Leu Ser Ala Lys Leu Ile Ala Ile Ser Ser Leu
180     185     190
Ser Val Val Leu Ala Ser Ile Val Ala Met Cys Val His Ser Met Ser
195     200     205
Glu Phe Gln Asn Glu Asp Gly Glu Val Asp Asp Pro Val Leu Glu Gly
210     215     220
Val Glu Ile Ala Cys Ile Ala Trp Phe Thr Gly Glu Leu Ala Val Arg
225     230     235     240
Leu Ala Ala Ala Pro Cys Gln Lys Lys Phe Trp Lys Asn Pro Leu Asn
245     250     255
Ile Ile Asp Phe Val Ser Ile Ile Pro Phe Tyr Ala Thr Leu Ala Val
260     265     270
Asp Thr Lys Glu Glu Glu Ser Glu Asp Ile Glu Asn Met Gly Lys Val
275     280     285
Val Gln Ile Leu Arg Leu Met Arg Ile Phe Arg Ile Leu Lys Leu Ala
290     295     300
Arg His Ser Val Gly Leu Arg Ser Leu Gly Ala Thr Leu Arg His Ser
305     310     315     320
Tyr His Glu Val Gly Leu Leu Leu Leu Phe Leu Ser Val Gly Ile Ser
325     330     335
Ile Phe Ser Val Leu Ile Tyr Ser Val Glu Lys Asp Asp His Thr Ser
340     345     350

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Ser Leu Thr Ser Ile Pro Ile Cys Trp Trp Trp Ala Thr Ile Ser Met
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Thr Thr Val Gly Tyr Gly Asp Thr His Pro Val Thr Leu Ala Gly Lys
      370              375              380
Leu Ile Ala Ser Thr Cys Ile Ile Cys Gly Ile Leu Val Val Ala Leu
385              390              395              400
Pro Ile Thr Ile Ile Phe Asn Lys Phe Ser Lys Tyr Tyr Gln Lys Gln
      405              410              415
Lys Asp Ile Asp Val Asp Gln Cys Ser Glu Asp Ala Pro Glu Lys Cys
      420              425              430
His Glu Leu Pro Tyr Phe Asn Ile Arg Asp Ile Tyr Ala Gln Arg Met
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His Ala Phe Ile Thr Ser Leu Ser Ser Val Gly Ile Val Val Ser Asp
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cagggactgt gtcgggcttg gacctcacct gatectctct cttagcgcca cccttctct 240
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cggcaggagg aggaaggcgc acagcgggtg gagagggtgc gccaaaggaga ggtaaccct 360
tcgggagccc ggggaatccc ggccgccacc aggggccgtg ccaccgccct cgcgggacca 420
aagcttccgg cgtgtcccca actttgtggc gccctcaggc cgcggcgact gggttagag 479
atg cct tcc agc ggc aga gcg ctg ctg gac tcg ccg ctg gac agc ggc 527
Met Pro Ser Ser Gly Arg Ala Leu Leu Asp Ser Pro Leu Asp Ser Gly
  1              5              10              15

tcc ctg acc tcc ctg gac tct agt gtc ttc tgc agc gag ggt gaa ggg 575
Ser Leu Thr Ser Leu Asp Ser Ser Val Phe Cys Ser Glu Gly Glu Gly
      20              25              30

gag ccc ttg gcg ctc ggg gac tgc ttc acg gtc aac gtg ggc ggc agc 623
Glu Pro Leu Ala Leu Gly Asp Cys Phe Thr Val Asn Val Gly Gly Ser
      35              40              45

cgc ttc gtg ctc tcg cag cag gcg ctg tcc tgc ttc ccg cac acg cgc 671
Arg Phe Val Leu Ser Gln Gln Ala Leu Ser Cys Phe Pro His Thr Arg
      50              55              60

ctt ggc aag ctg gcc gtg gtg gtg gct tcc tac cgc cgc ccc ggg gcc 719
Leu Gly Lys Leu Ala Val Val Val Ala Ser Tyr Arg Arg Pro Gly Ala
      65              70              75              80

ctg gcc gcc gtg ccc agc cct ctg gag ctt tgc gac gat gcc aac ccc 767
Leu Ala Ala Val Pro Ser Pro Leu Glu Leu Cys Asp Asp Ala Asn Pro
      85              90              95

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gtg gac aac gag tac ttc ttc gac cgc agc tcg cag gcg ttc cga tat	815
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Val Leu His Tyr Tyr Arg Thr Gly Arg Leu His Val Met Glu Gln Leu	
115 120 125	
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Cys Ala Leu Ser Phe Leu Gln Glu Ile Gln Tyr Trp Gly Ile Asp Glu	
130 135 140	
ctc agc atc gat tcc tgc tgc agg gac aga tac ttc aga agg aaa gag	959
Leu Ser Ile Asp Ser Cys Cys Arg Asp Arg Tyr Phe Arg Arg Lys Glu	
145 150 155 160	
ctg agt gaa act tta gac ttc aag aag gac aca gaa gac cag gaa agt	1007
Leu Ser Glu Thr Leu Asp Phe Lys Lys Asp Thr Glu Asp Gln Glu Ser	
165 170 175	
caa cat gag agt gaa cag gac ttc tcc caa gga cct tgt ccc act gtt	1055
Gln His Glu Ser Glu Gln Asp Phe Ser Gln Gly Pro Cys Pro Thr Val	
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Arg Gln Lys Leu Trp Asn Ile Leu Glu Lys Pro Gly Ser Ser Thr Ala	
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Ala Arg Ile Phe Gly Val Ile Ser Ile Ile Phe Val Val Val Ser Ile	
210 215 220	
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Ile Asn Met Ala Leu Met Ser Ala Glu Leu Ser Trp Leu Asp Leu Gln	
225 230 235 240	
ctg ctg gaa atc ctg gag tat gtg tgc att agc tgg ttc acc ggg gag	1247
Leu Leu Glu Ile Leu Glu Tyr Val Cys Ile Ser Trp Phe Thr Gly Glu	
245 250 255	
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Phe Val Leu Arg Phe Leu Cys Val Arg Asp Arg Cys Arg Phe Leu Arg	
260 265 270	
aag gtg cca aac atc ata gac ctc ctt gcc atc ttg ccc ttc tac atc	1343
Lys Val Pro Asn Ile Ile Asp Leu Leu Ala Ile Leu Pro Phe Tyr Ile	
275 280 285	
act ctt ctg gta gag agc cta agt ggg agc cag acc acg cag gag ctg	1391
Thr Leu Leu Val Glu Ser Leu Ser Gly Ser Gln Thr Thr Gln Glu Leu	
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gag aac gtg ggg cgc att gtc cag gtg ttg agg ctg ctc agg gct ctg	1439
Glu Asn Val Gly Arg Ile Val Gln Val Leu Arg Leu Leu Arg Ala Leu	
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cgc atg cta aag ctg ggc aga cat tcc aca gga tta cgc tcc ctt ggg	1487
Arg Met Leu Lys Leu Gly Arg His Ser Thr Gly Leu Arg Ser Leu Gly	
325 330 335	

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 Met Thr Ile Thr Gln Cys Tyr Glu Glu Val Gly Leu Leu Leu Leu Phe
 340 345 350

cta tcc gtg gga atc tct ata ttt tca act gta gaa tac ttt gct gag 1583
 Leu Ser Val Gly Ile Ser Ile Phe Ser Thr Val Glu Tyr Phe Ala Glu
 355 360 365

caa agc att cct gac aca acc ttc aca agt gtc cct tgt gca tgg tgg 1631
 Gln Ser Ile Pro Asp Thr Thr Phe Thr Ser Val Pro Cys Ala Trp Trp
 370 375 380

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 Trp Ala Thr Thr Ser Met Thr Thr Val Gly Tyr Gly Asp Ile Arg Pro
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 Asp Thr Thr Thr Gly Lys Ile Val Ala Phe Met Cys Ile Leu Ser Gly
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 Ile Leu Val Leu Ala Leu Pro Ile Ala Ile Ile Asn Asp Arg Phe Ser
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 Asp Phe Trp

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3080

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<213> H. sapiens

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 Val Leu His Tyr Tyr Arg Thr Gly Arg Leu His Val Met Glu Gln Leu
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 Cys Ala Leu Ser Phe Leu Gln Glu Ile Gln Tyr Trp Gly Ile Asp Glu
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 Gln His Glu Ser Glu Gln Asp Phe Ser Gln Gly Pro Cys Pro Thr Val
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 Arg Gln Lys Leu Trp Asn Ile Leu Glu Lys Pro Gly Ser Ser Thr Ala
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 Ala Arg Ile Phe Gly Val Ile Ser Ile Ile Phe Val Val Val Ser Ile
 210 215 220
 Ile Asn Met Ala Leu Met Ser Ala Glu Leu Ser Trp Leu Asp Leu Gln
 225 230 235 240
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 Phe Val Leu Arg Phe Leu Cys Val Arg Asp Arg Cys Arg Phe Leu Arg
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 Lys Val Pro Asn Ile Ile Asp Leu Ala Ile Leu Pro Phe Tyr Ile
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 Thr Leu Leu Val Glu Ser Leu Ser Gly Ser Gln Thr Thr Gln Glu Leu
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 325 330 335
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 340 345 350
 Leu Ser Val Gly Ile Ser Ile Phe Ser Thr Val Glu Tyr Phe Ala Glu
 355 360 365
 Gln Ser Ile Pro Asp Thr Thr Phe Thr Ser Val Pro Cys Ala Trp Trp
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 Trp Ala Thr Thr Ser Met Thr Thr Val Gly Tyr Gly Asp Ile Arg Pro
 385 390 395 400
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 405 410 415
 Ile Leu Val Leu Ala Leu Pro Ile Ala Ile Ile Asn Asp Arg Phe Ser

420 425 430
 Ala Cys Tyr Phe Thr Leu Lys Leu Lys Glu Ala Ala Val Arg Gln Arg
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 Glu Ala Leu Lys Lys Leu Thr Lys Asn Ile Ala Thr Asp Ser Tyr Ile
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 cccaccatcc tggagacagc cacattctcc taaacgccac cctcactaag tctcctggg 240
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 Met Ala Ala Gly Leu Ala Thr Trp Leu Pro Phe Ala
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 Arg Ala Ala Ala Val Gly Trp Leu Pro Pro Ala Gln Gln Pro Leu Pro
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 ccg gca ccg ggg gtg aag gca tct cga gga gat grg gtt ctg gtg gtg 388
 Pro Ala Pro Gly Val Lys Ala Ser Arg Gly Asp Xaa Val Leu Val Val
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 aac gtg agc gga ccg cgc ttt gag act tgg aag aat acg ctg gac cgc 436
 Asn Val Ser Gly Arg Arg Phe Glu Thr Trp Lys Asn Thr Leu Asp Arg
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 tac cca gac acc ttg ctg ggc agc tcg gag aag gaa ttc ttc tac gat 484
 Tyr Pro Asp Thr Leu Leu Gly Ser Ser Glu Lys Glu Phe Phe Tyr Asp
 65 70 75

 gct gac tca ggc gag tac ttc ttc gat cgc gac cct gac atg ttc cgc 532
 Ala Asp Ser Gly Glu Tyr Phe Phe Asp Arg Asp Pro Asp Met Phe Arg
 80 85 90

 cat gtg ctg aac ttc tac cga acg ggg cgg ctg cat tgc cca cgg cag 580
 His Val Leu Asn Phe Tyr Arg Thr Gly Arg Leu His Cys Pro Arg Gln
 95 100 105

 gag tgc atc cag gcc ttc gac gaa gag ctg gct ttc tac ggc ctg gtt 628
 Glu Cys Ile Gln Ala Phe Asp Glu Glu Leu Ala Phe Tyr Gly Leu Val
 110 115 120

 ccc gag cta gtc ggt gac tgc tgc ctt gaa gag tat cgg gac cga aag 676
 Pro Glu Leu Val Gly Asp Cys Cys Leu Glu Tyr Arg Asp Arg Lys

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aag gag aat gcc gag cgc ctg gca gag gat gag gag gca gag cag gcc				724
Lys Glu Asn Ala Glu Arg Leu Ala Glu Asp Glu Glu Ala Glu Gln Ala				
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ggg gac ggc cca gcc ctg cca gca ggc agc tcc ctg cgg cag cgg ctc				772
Gly Asp Gly Pro Ala Leu Pro Ala Gly Ser Ser Leu Arg Gln Arg Leu				
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Trp Arg Ala Phe Glu Asn Pro His Thr Ser Thr Ala Ala Leu Val Phe				
	175	180	185	
tac tat gtg acc ggc ttc ttc atc gcc gtg tgc gtc atc gcc aat gtg				868
Tyr Tyr Val Thr Gly Phe Phe Ile Ala Val Ser Val Ile Ala Asn Val				
	190	195	200	
gtg gag acc atc cca tgc cgc ggc tct gca cgc agg tcc tca agg gag				916
Val Glu Thr Ile Pro Cys Arg Gly Ser Ala Arg Arg Ser Ser Arg Glu				
	205	210	215	220
cag ccc tgt ggc gaa cgc ttc cca cag gcc ttt ttc tgc atg gac aca				964
Gln Pro Cys Gly Glu Arg Phe Pro Gln Ala Phe Phe Cys Met Asp Thr				
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gcc tgt gta ctc ata ttc aca ggt gaa tac ctc ctg cgg ctg ttt gcc				1012
Ala Cys Val Leu Ile Phe Thr Gly Glu Tyr Leu Leu Arg Leu Phe Ala				
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gcc_ccc agc cgt tgc cgc ttc ctg cgg agt gtc atg agc ctc atc gac				1060
Ala Pro Ser Arg Cys Arg Phe Leu Arg Ser Val Met Ser Leu Ile Asp				
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gtg gtg gcc atc ctg ccc tac tac att ggg ctt ttg gtg ccc aag aac				1108
Val Val Ala Ile Leu Pro Tyr Tyr Ile Gly Leu Leu Val Pro Lys Asn				
	270	275	280	
gac gat gtc tct ggc gcc ttt gtc acc ctg cgt gtg ttc cgg gtg ttt				1156
Asp Asp Val Ser Gly Ala Phe Val Thr Leu Arg Val Phe Arg Val Phe				
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cgc atc ttc aag ttc tcc agg cac tca cag ggc ttg agg att ctg ggc				1204
Arg Ile Phe Lys Phe Ser Arg His Ser Gln Gly Leu Arg Ile Leu Gly				
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tac aca ctc aag agc tgt gcc tct gag ctg ggc ttt ctc ctc ttt tcc				1252
Tyr Thr Leu Lys Ser Cys Ala Ser Glu Leu Gly Phe Leu Leu Phe Ser				
	320	325	330	
cta acc atg gcc atc atc atc ttt gcc act gtc atg ttt tat gct gag				1300
Leu Thr Met Ala Ile Ile Ile Phe Ala Thr Val Met Phe Tyr Ala Glu				
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Lys Gly Thr Asn Lys Thr Asn Phe Thr Ser Ile Pro Ala Ala Phe Trp				
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tat acc att gtc acc atg acc acg ctt ggc tac gga gac atg gtg ccc				1396
Tyr Thr Ile Val Thr Met Thr Thr Leu Gly Tyr Gly Asp Met Val Pro				
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465 470 475	
caa cat cac cac ttg ctg cac tgt cta gag aag aca acg tgc cat gag Gln His His His Leu Leu His Cys Leu Glu Lys Thr Thr Cys His Glu	1732
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495 500 505	
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525 530 535 540	
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agc cgc tcc agc ctc aat gcc aag ccc cat gac agc ctt gac ctg aac Ser Arg Ser Ser Leu Asn Ala Lys Pro His Asp Ser Leu Asp Leu Asn	2020
575 580 585	
tgc gac agc cgg gac ttc gtg gct gcc att atc agc atc cct acc cct Cys Asp Ser Arg Asp Phe Val Ala Ala Ile Ile Ser Ile Pro Thr Pro	2068
590 595 600	
cct gcc aac acc cca gat gag agc caa cct tcc tcc cct ggc ggc ggt Pro Ala Asn Thr Pro Asp Glu Ser Gln Pro Ser Ser Pro Gly Gly Gly	2116
605 610 615 620	

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 65 70 75 80
 Glu Tyr Phe Phe Asp Arg Asp Pro Asp Met Phe Arg His Val Leu Asn
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 Phe Tyr Arg Thr Gly Arg Leu His Cys Pro Arg Gln Glu Cys Ile Gln
 100 105 110
 Ala Phe Asp Glu Glu Leu Ala Phe Tyr Gly Leu Val Pro Glu Leu Val
 115 120 125
 Gly Asp Cys Cys Leu Glu Glu Tyr Arg Asp Arg Lys Lys Glu Asn Ala
 130 135 140
 Glu Arg Leu Ala Glu Asp Glu Glu Ala Glu Gln Ala Gly Asp Gly Pro
 145 150 155 160

Ala Leu Pro Ala Gly Ser Ser Leu Arg Gln Arg Leu Trp Arg Ala Phe
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 Glu Asn Pro His Thr Ser Thr Ala Ala Leu Val Phe Tyr Tyr Val Thr
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 Gly Phe Phe Ile Ala Val Ser Val Ile Ala Asn Val Val Glu Thr Ile
 195 200 205
 Pro Cys Arg Gly Ser Ala Arg Arg Ser Ser Arg Glu Gln Pro Cys Gly
 210 215 220
 Glu Arg Phe Pro Gln Ala Phe Phe Cys Met Asp Thr Ala Cys Val Leu
 225 230 235 240
 Ile Phe Thr Gly Glu Tyr Leu Leu Arg Leu Phe Ala Ala Pro Ser Arg
 245 250 255
 Cys Arg Phe Leu Arg Ser Val Met Ser Leu Ile Asp Val Val Ala Ile
 260 265 270
 Leu Pro Tyr Tyr Ile Gly Leu Leu Val Pro Lys Asn Asp Asp Val Ser
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 Gly Ala Phe Val Thr Leu Arg Val Phe Arg Val Phe Arg Ile Phe Lys
 290 295 300
 Phe Ser Arg His Ser Gln Gly Leu Arg Ile Leu Gly Tyr Thr Leu Lys
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 Ser Cys Ala Ser Glu Leu Gly Phe Leu Leu Phe Ser Leu Thr Met Ala
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 Ile Ile Ile Phe Ala Thr Val Met Phe Tyr Ala Glu Lys Gly Thr Asn
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 Lys Thr Asn Phe Thr Ser Ile Pro Ala Ala Phe Trp Tyr Thr Ile Val
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 Tyr Lys Gln Asn Gly Gly Leu Glu Asp Ser Gly Ser Gly Glu Glu Gln
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 595 600 605
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15 20 25

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tta tac att act caa aaa caa aca ctg acc aag tac cca gac act ttc 556
Leu Tyr Ile Thr Gln Lys Gln Thr Leu Thr Lys Tyr Pro Asp Thr Phe
 45 50 55

ctt gaa ggt ata gta aat gga aaa atc ctc tgc ccg ttt gat gct gat 604
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60 65 70

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 Gly His Tyr Phe Ile Asp Arg Asp Gly Leu Leu Phe Arg His Val Leu
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Asn Phe Leu Arg Asn Gly Glu Leu Leu Leu Pro Glu Gly Phe Arg Glu
95 100 105

aat caa ctt ctt gca caa gaa gca gaa ttc ttt cag ctc aag gga ctg 748
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gca gag gaa gtg aaa tcc agg tgg gag aaa gaa cag cta aca ccc aga 796
Ala Glu Glu Val Lys Ser Arg Trp Glu Lys Glu Gln Leu Thr Pro Arg
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gag act act ttc ttg gaa ata aca gat aac cac gat cgt tca caa gga 844
Glu Thr Thr Phe Leu Glu Ile Thr Asp Asn His Asp Arg Ser Gln Gly
140 145 150

tta aga atc ttc tgt aat gct cct gat ttc ata tca aaa ata aag tct 892
Leu Arg Ile Phe Cys Asn Ala Pro Asp Phe Ile Ser Lys Ile Lys Ser


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cgc att gtt ctg gtg tcc aaa agc agg ctg gat gga ttt cca gag gag      940
Arg Ile Val Leu Val Ser Lys Ser Arg Leu Asp Gly Phe Pro Glu Glu
          175          180          185

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Phe Ser Ile Ser Ser Asn Ile Ile Gln Phe Lys Tyr Phe Ile Lys Ser
          190          195          200

gaa aat ggc act cga ctt gta cta aag gaa gac aac acc ttt gtc tgt      1036
Glu Asn Gly Thr Arg Leu Val Leu Lys Glu Asp Asn Thr Phe Val Cys
          205          210          215

acc ttg gaa act ctt aag ttt gag gct atc atg atg gct tta aag tgt      1084
Thr Leu Glu Thr Leu Lys Phe Glu Ala Ile Met Met Ala Leu Lys Cys
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ggc ttt aga ctg ctg acc agc ctg gat tgt tcc aaa ggg tca att gtt      1132
Gly Phe Arg Leu Leu Thr Ser Leu Asp Cys Ser Lys Gly Ser Ile Val
          235          240          245          250

cac agc gat gca ctt cat ttt atc a agtaattacc tgtgtcacga      1177
His Ser Asp Ala Leu His Phe Ile
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acaaaaggcaa caagcatgca gccagcaagc ttcggaaaac cacagcatca aagacatccc      1237
aaataacatg cccagctagc tctgtactac agagccctgc tactaatcaa ttactgtgag      1297
ctaacgggat gtaaattcta tcgctaaaga tgccttcct ctggggtgtt cctactgac      1357
agactcttcc acctaaaatg aaaacagtaa ccttctatat actgtaaaata aagactgaaa      1417
gcttttgcta tttatttgtc cttaagctgt ctttcaattc agattgtctt gggatattgc      1477
acaaaaagaa gcatgtacat tatctatcgt tcatttaagt aaatggtaat aaaatatattt      1537
aaggggctat taatatattaa aatccttttc tactatggca aaaatctaca gagaaactga      1597
actggcaaaa ttaactacct ggagcaaaac agatgtgcag atctaactaa aacagagcta      1657
tagtgaaaca aaatgagatt gtaagaagac attaaagcta ttgatttgat ttttccatag      1717
caagcaccaa aagcttatat tcacagttcc tgtgtttcat attagactta tagctgaatt      1777
ggtattttgc tgaataattcc tagaaaactg cttgatgaca ataaaaagta aataaaagca      1837
ctgctacctt caaaaaaaaaa aaaaa      1862

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<210> 12
 <211> 258
 <212> PRT
 <213> H. sapiens

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<400> 12
Met Glu Arg Lys Ile Asn Arg Arg Glu Lys Glu Lys Glu Tyr Glu Gly
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Lys His Asn Ser Leu Glu Asp Thr Asp Gln Gly Lys Asn Cys Lys Ser
          20          25          30
Thr Leu Met Thr Leu Asn Val Gly Gly Tyr Leu Tyr Ile Thr Gln Lys
          35          40          45
Gln Thr Leu Thr Lys Tyr Pro Asp Thr Phe Leu Glu Gly Ile Val Asn
          50          55          60
Gly Lys Ile Leu Cys Pro Phe Asp Ala Asp Gly His Tyr Phe Ile Asp
65          70          75          80
Arg Asp Gly Leu Leu Phe Arg His Val Leu Asn Phe Leu Arg Asn Gly
          85          90          95
Glu Leu Leu Leu Pro Glu Gly Phe Arg Glu Asn Gln Leu Leu Ala Gln
          100          105          110
Glu Ala Glu Phe Phe Gln Leu Lys Gly Leu Ala Glu Glu Val Lys Ser
          115          120          125

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Arg Trp Glu Lys Glu Gln Leu Thr Pro Arg Glu Thr Thr Phe Leu Glu
 130 135 140
 Ile Thr Asp Asn His Asp Arg Ser Gln Gly Leu Arg Ile Phe Cys Asn
 145 150 155 160
 Ala Pro Asp Phe Ile Ser Lys Ile Lys Ser Arg Ile Val Leu Val Ser
 165 170 175
 Lys Ser Arg Leu Asp Gly Phe Pro Glu Glu Phe Ser Ile Ser Ser Asn
 180 185 190
 Ile Ile Gln Phe Lys Tyr Phe Ile Lys Ser Glu Asn Gly Thr Arg Leu
 195 200 205
 Val Leu Lys Glu Asp Asn Thr Phe Val Cys Thr Leu Glu Thr Leu Lys
 210 215 220
 Phe Glu Ala Ile Met Met Ala Leu Lys Cys Gly Phe Arg Leu Leu Thr
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 Ser Leu Asp Cys Ser Lys Gly Ser Ile Val His Ser Asp Ala Leu His
 245 250 255
 Phe Ile

<210> 13
 <211> 1877
 <212> DNA
 <213> H. sapiens

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 <222> (322)...(1090)
 <223> K+Hnov27

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 gtcgggccc acgtgaaatc cgaggctgcg cccaagcgcg ccctgtacga gtctgtgttc 120
 gggtcgggg aaatctgctg cccacttcc ccaaaagac tttgtatccg cccctcggag 180
 cctgtggatg cgggtggtgt ggtttccgtg aaacacgacc ccctgcctct tcttcagaa 240
 gccaatgggc acagaagcac caattctccc acaatagttt cacctgctat tgtttccccc 300
 acccaggaca gtcggcccaa t atg tca aga cct ctg atc act aga tcc cct 351
 Met Ser Arg Pro Leu Ile Thr Arg Ser Pro
 1 5 10
 gca tct cca ctg awc aac caa ggc atc cct act cca gca caa ctc aca 399
 Ala Ser Pro Leu Xaa Asn Gln Gly Ile Pro Thr Pro Ala Gln Leu Thr
 15 20 25
 aaa tcc aat gcg cct gtc cac att gat gtg ggc ggc cac atg tac acc 447
 Lys Ser Asn Ala Pro Val His Ile Asp Val Gly Gly His Met Tyr Thr
 30 35 40
 agc agc ctg gcc acc ctc acc aaa tac cct gaa tcc aga atc gga aga 495
 Ser Ser Leu Ala Thr Leu Thr Lys Tyr Pro Glu Ser Arg Ile Gly Arg
 45 50 55
 ctt ttt gat ggt aca gag ccc att gtt ttg gac agt ctc aaa cag cac 543
 Leu Phe Asp Gly Thr Glu Pro Ile Val Leu Asp Ser Leu Lys Gln His
 60 65 70
 tat ttc att gac aga gat gga cag atg ttc aga tat atc ttg aat ttt 591
 Tyr Phe Ile Asp Arg Asp Gly Gln Met Phe Arg Tyr Ile Leu Asn Phe
 75 80 85 90
 cta cga aca tcc aaa ctc ctc att cct gat gat ttc aag gac tac act 639
 Leu Arg Thr Ser Lys Leu Leu Ile Pro Asp Asp Phe Lys Asp Tyr Thr

95	100	105	
ttg tta tat gaa gag gca aaa tat ttt cag ctt cag ccc atg ttg ttg			687
Leu Leu Tyr Glu Glu Ala Lys Tyr Phe Gln Leu Gln Pro Met Leu Leu			
110	115	120	
gag atg gaa aga tgg aag cag gac aga gaa act ggt cga ttt tca agg			735
Glu Met Glu Arg Trp Lys Gln Asp Arg Glu Thr Gly Arg Phe Ser Arg			
125	130	135	
ccc tgt gag tgc ctc gtc gtg cgt gtg gcc cca gac ctc gga gaa agg			783
Pro Cys Glu Cys Leu Val Val Arg Val Ala Pro Asp Leu Gly Glu Arg			
140	145	150	
atc acg cta agc ggt gac aaa tcc ttg ata gaa gaa gta ttt cca gag			831
Ile Thr Leu Ser Gly Asp Lys Ser Leu Ile Glu Glu Val Phe Pro Glu			
155	160	165	170
atc ggc gac gtg atg tgt aac tct gtc aat gca ggc tgg aat cac gac			879
Ile Gly Asp Val Met Cys Asn Ser Val Asn Ala Gly Trp Asn His Asp			
175	180	185	
tcg acg cac gtc atc agg ttt cca cta aat ggc tac tgt cac ctc aac			927
Ser Thr His Val Ile Arg Phe Pro Leu Asn Gly Tyr Cys His Leu Asn			
190	195	200	
tca gtc cag gtc ctc gag agg ttg cag caa aga gga ttt gaa atc gtg			975
Ser Val Gln Val Leu Glu Arg Leu Gln Gln Arg Gly Phe Glu Ile Val			
205	210	215	
ggc tcc tgt ggg gga gga gta gac tcg tcc cag ttc agc gaa tac gtc			1023
Gly Ser Cys Gly Gly Gly Val Asp Ser Ser Gln Phe Ser Glu Tyr Val			
220	225	230	
ctt cgg cgg gaa ctg agg cgg acg ccc cgt gta ccc tcc gtc atc cgg			1071
Leu Arg Arg Glu Leu Arg Arg Thr Pro Arg Val Pro Ser Val Ile Arg			
235	240	245	250
ata aag caa gag cct ctg g actaaatgga catatttctt atgcaaaaag			1120
Ile Lys Gln Glu Pro Leu			
255			
gaaaacacac acaaccaata actcaaacaa aaaaggagaca tttatgtgca gttgggacag			1180
caaaccaagt cctggacgta aaattgaata aaagacacat ttatatccaa tagagaccac			1240
acctgtattc atatgggaac aattggaata gtgatatcct caagggtgtaa aaaatatata			1300
aatatatata tatatgtcaa aaggtaggaa atgcaaaaaa gaaaaaaaaa aaagggtgaca			1360
gccgcagttg gtgctgtgat ggccgtgaag tgtcctgggc ctcccagggc ctctgacaaa			1420
taacaagcc atgagtgggtg aggacacagt ctccctacag tttccattgc caacaacagc			1480
catccatatt tcttttttcc tttgtctttc tttttccttt ttttttaaaa aaacaaaaca			1540
aacaaaacac cttgaatcaa gtttgtttgt atatggaggt tccacgtctt tctttaggca			1600
gggaccaggc aggacttcag aaaaaccctc atgagcacat tgcaaagatg ttagacatga			1660
aatttttaaat gtagtttgta cagaagtcac acttttttgt ccacctcaca gatgtgaact			1720
ttactttgtt ttaaaactga tcagttttgc caaggggcca gaattattcc ttgttagaat			1780
tgctccagtt caagtctgct gctttcctac aatttttcaa attttataat gtattaaata			1840
caataaactc tgttttaaaaa ataaaaaaaa aaaaaaa			1877

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<211> 256

<212> PRT

<213> H. sapiens

<220>
 <221> VARIANT
 <222> (1)...(256)
 <223> Xaa = Any Amino Acid

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 Gln Gly Ile Pro Thr Pro Ala Gln Leu Thr Lys Ser Asn Ala Pro Val
 20 25 30
 His Ile Asp Val Gly Gly His Met Tyr Thr Ser Ser Leu Ala Thr Leu
 35 40 45
 Thr Lys Tyr Pro Glu Ser Arg Ile Gly Arg Leu Phe Asp Gly Thr Glu
 50 55 60
 Pro Ile Val Leu Asp Ser Leu Lys Gln His Tyr Phe Ile Asp Arg Asp
 65 70 75 80
 Gly Gln Met Phe Arg Tyr Ile Leu Asn Phe Leu Arg Thr Ser Lys Leu
 85 90 95
 Leu Ile Pro Asp Asp Phe Lys Asp Tyr Thr Leu Leu Tyr Glu Glu Ala
 100 105 110
 Lys Tyr Phe Gln Leu Gln Pro Met Leu Leu Glu Met Glu Arg Trp Lys
 115 120 125
 Gln Asp Arg Glu Thr Gly Arg Phe Ser Arg Pro Cys Glu Cys Leu Val
 130 135 140
 Val Arg Val Ala Pro Asp Leu Gly Glu Arg Ile Thr Leu Ser Gly Asp
 145 150 155 160
 Lys Ser Leu Ile Glu Glu Val Phe Pro Glu Ile Gly Asp Val Met Cys
 165 170 175
 Asn Ser Val Asn Ala Gly Trp Asn His Asp Ser Thr His Val Ile Arg
 180 185 190
 Phe Pro Leu Asn Gly Tyr Cys His Leu Asn Ser Val Gln Val Leu Glu
 195 200 205
 Arg Leu Gln Gln Arg Gly Phe Glu Ile Val Gly Ser Cys Gly Gly Gly
 210 215 220
 Val Asp Ser Ser Gln Phe Ser Glu Tyr Val Leu Arg Arg Glu Leu Arg
 225 230 235 240
 Arg Thr Pro Arg Val Pro Ser Val Ile Arg Ile Lys Gln Glu Pro Leu
 245 250 255

<210> 15
 <211> 923
 <212> DNA
 <213> H. sapiens

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 <223> K+Hnov2

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 gaacccggggc ggcgaagggt gagtgagccg agattgcacc actgcactcc agcctggggcg 120
 acagagcgag actccatctc aaaaaaaga gtagttatgg ccac atg gcc cca cta 176
 Met Ala Pro Leu
 1
 tcg cca ggc gga aag gcc ttc tgc atg gtc tat gca gcc ctg ggg ctg 224
 Ser Pro Gly Gly Lys Ala Phe Cys Met Val Tyr Ala Ala Leu Gly Leu
 5 10 15 20
 cca gcc tcc tta gct ctc gtg gcc acc ctg cgc cat tgc ctg ctg cct 272

Pro Ala Ser Leu Ala Leu Val Ala Thr Leu Arg His Cys Leu Leu Pro
25 30 35

gtg ctc agc cgc cca cgt gcc tgg gta gcg gtc cac tgg cag ctg tca 320
Val Leu Ser Arg Pro Arg Ala Trp Val Ala Val His Trp Gln Leu Ser
40 45 50

ccg gcc agg gct gcg ctg ctg cag gca gtt gca ctg gga ctg ctg gtg 368
Pro Ala Arg Ala Ala Leu Leu Gln Ala Val Ala Leu Gly Leu Leu Val
55 60 65

gcc agc agc ttt gtg ctg ctg cca gcg ctg gtg ctg tgg ggc ctt cag 416
Ala Ser Ser Phe Val Leu Leu Pro Ala Leu Val Leu Trp Gly Leu Gln
70 75 80

ggc gac tgc agc ctg ctg ggg gcc gtc tac ttc tgc ttc agc tcg ctc 464
Gly Asp Cys Ser Leu Leu Gly Ala Val Tyr Phe Cys Phe Ser Ser Leu
85 90 95 100

agc acc att ggc ctg gag gac ttg ctg ccc ggc cgc ggc cgc agc ctg 512
Ser Thr Ile Gly Leu Glu Asp Leu Leu Pro Gly Arg Gly Arg Ser Leu
105 110 115

cac ccc gtg att tac cac ctg ggc cag ctc gca ctt ctt ggt tac ttg 560
His Pro Val Ile Tyr His Leu Gly Gln Leu Ala Leu Leu Gly Tyr Leu
120 125 130

ctt cta gga ctc ttg gcc atg ctg ctg gca gtg gag acc ttc tct gag 608
Leu Leu Gly Leu Leu Ala Met Leu Leu Ala Val Glu Thr Phe Ser Glu
135 140 145

ctg ccg cag gtc cgt gcc atg ggg aag ttc ttc aga ccc agt ggt cct 656
Leu Pro Gln Val Arg Ala Met Gly Lys Phe Phe Arg Pro Ser Gly Pro
150 155 160

gtg act gct gag gac caa ggt ggc atc cta ggg cag gat gaa ctg gct 704
Val Thr Ala Glu Asp Gln Gly Gly Ile Leu Gly Gln Asp Glu Leu Ala
165 170 175 180

ctg agc acc ctg ccg ccc gcg gcc cca gct tca gga caa gcc cct gct 752
Leu Ser Thr Leu Pro Pro Ala Ala Pro Ala Ser Gly Gln Ala Pro Ala
185 190 195

tgc t gaagcgtcag gtgaccgagt tcagctccgt aaggtggcgg cacctgagga 806
Cys

ggaagcagcc aggagtggct ggggaagaat ctggagatgg agccgcggtg aggggtggcg 866
ggaggcctca ggggatactg ttaatcataa aaaaaaaaaa aaaaaaaaaa aaaaaaa 923

<210> 16

<211> 197

<212> PRT

<213> H. sapiens

<400> 16

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20 25 30
Cys Leu Leu Pro Val Leu Ser Arg Pro Arg Ala Trp Val Ala Val His

35 40 45
 Trp Gln Leu Ser Pro Ala Arg Ala Ala Leu Leu Gln Ala Val Ala Leu
 50 55 60
 Gly Leu Leu Val Ala Ser Ser Phe Val Leu Leu Pro Ala Leu Val Leu
 65 70 75 80
 Trp Gly Leu Gln Gly Asp Cys Ser Leu Leu Gly Ala Val Tyr Phe Cys
 85 90 95
 Phe Ser Ser Leu Ser Thr Ile Gly Leu Glu Asp Leu Leu Pro Gly Arg
 100 105 110
 Gly Arg Ser Leu His Pro Val Ile Tyr His Leu Gly Gln Leu Ala Leu
 115 120 125
 Leu Gly Tyr Leu Leu Leu Gly Leu Leu Ala Met Leu Leu Ala Val Glu
 130 135 140
 Thr Phe Ser Glu Leu Pro Gln Val Arg Ala Met Gly Lys Phe Phe Arg
 145 150 155 160
 Pro Ser Gly Pro Val Thr Ala Glu Asp Gln Gly Gly Ile Leu Gly Gln
 165 170 175
 Asp Glu Leu Ala Leu Ser Thr Leu Pro Pro Ala Ala Pro Ala Ser Gly
 180 185 190
 Gln Ala Pro Ala Cys
 195

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 <211> 3102
 <212> DNA
 <213> H. sapiens

<220>
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 <222> (274)...(1705)
 <223> K+Hnov11

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 ttcagcaccc aagaccacc aggaggcctg ggcccgccag taatgggtag ggagaggggg 180
 ccccgccagg gcgcacggcg ctctcgccga cgctgttccc tccgcttcca ggtgtagcgc 240
 ccccgcgagg cgcgggcggc cggcgccctcc agc atg acc ggc cag agc ctg tgg 294
 Met Thr Gly Gln Ser Leu Trp
 1 5
 gac gtg tog gag gct aac gtc gag gac ggg gag atc cgc atc aat gtg 342
 Asp Val Ser Glu Ala Asn Val Glu Asp Gly Glu Ile Arg Ile Asn Val
 10 15 20
 ggc ggc ttc aag agg agg ctg cgc tcg cac acg ctg ctg cgc ttc ccc 390
 Gly Gly Phe Lys Arg Arg Leu Arg Ser His Thr Leu Leu Arg Phe Pro
 25 30 35
 gag acg cgc ctg ggc cgc ttg ctg ctc tgc cac tcg cgc gag gcc att 438
 Glu Thr Arg Leu Gly Arg Leu Leu Leu Cys His Ser Arg Glu Ala Ile
 40 45 50 55
 ctg gag ctc tgc gat gac tac gac gac gtc cag cgg gag ttc tac ttc 486
 Leu Glu Leu Cys Asp Asp Tyr Asp Asp Val Gln Arg Glu Phe Tyr Phe
 60 65 70
 gac cgc aac cct gag ctc ttc ccc tac gtg ctg cat ttc tat cac acc 534
 Asp Arg Asn Pro Glu Leu Phe Pro Tyr Val Leu His Phe Tyr His Thr
 75 80 85

ggc aag ctt cac gtc atg gct gag cta tgt gtc ttc tcc ttc agc cag Gly Lys Leu His Val Met Ala Glu Leu Cys Val Phe Ser Phe Ser Gln 90 95 100	582
gag atc gag tac tgg ggc atc aac gag ttc ttc att gac tcc tgc tgc Glu Ile Glu Tyr Trp Gly Ile Asn Glu Phe Phe Ile Asp Ser Cys Cys 105 110 115	630
agc tac agc tac cat ggc cgc aaa gta gag ccc gag cag gag aag tgg Ser Tyr Ser Tyr His Gly Arg Lys Val Glu Pro Glu Gln Glu Lys Trp 120 125 130 135	678
gac gag cag agt gac cag gag agc acc acg tct tcc ttc gat gag atc Asp Glu Gln Ser Asp Gln Glu Ser Thr Thr Ser Ser Phe Asp Glu Ile 140 145 150	726
ctt gcc ttc tac aac gac gcc tcc aag ttc gat ggg cag ccc ctc ggc Leu Ala Phe Tyr Asn Asp Ala Ser Lys Phe Asp Gly Gln Pro Leu Gly 155 160 165	774
aac ttc cgc agg cag ctg tgg ctg gcg ctg gac aac ccc ggc tac tca Asn Phe Arg Arg Gln Leu Trp Leu Ala Leu Asp Asn Pro Gly Tyr Ser 170 175 180	822
gtg ctg agc agg gtc ttc agc atc ctg tcc atc ctg gtg gtg atg ggg Val Leu Ser Arg Val Phe Ser Ile Leu Ser Ile Leu Val Val Met Gly 185 190 195	870
tcc atc atc acc atg tgc ctc aat agc ctg ccc gat ttc caa atc cct Ser Ile Ile Thr Met Cys Leu Asn Ser Leu Pro Asp Phe Gln Ile Pro 200 205 210 215	918
gac agc cag ggc aac cct ggc gag gac cct agg ttc gaa atc gtg gag Asp Ser Gln Gly Asn Pro Gly Glu Asp Pro Arg Phe Glu Ile Val Glu 220 225 230	966
cac ttt ggc att gcc tgg ttc aca ttt gag ctg gtg gcc agg ttt gct His Phe Gly Ile Ala Trp Phe Thr Phe Glu Leu Val Ala Arg Phe Ala 235 240 245	1014
gtg gcc cct gac ttc ctc aag ttc ttc aag aat gcc cta aac ctt att Val Ala Pro Asp Phe Leu Lys Phe Phe Lys Asn Ala Leu Asn Leu Ile 250 255 260	1062
gac ctc atg tcc atc gtc ccc ttt tac atc act ctg gtg gtg aac ctg Asp Leu Met Ser Ile Val Pro Phe Tyr Ile Thr Leu Val Val Asn Leu 265 270 275	1110
gtg gtg gag agc aca cct act tta gcc aac ttg ggc agg gtg gcc cag Val Val Glu Ser Thr Pro Thr Leu Ala Asn Leu Gly Arg Val Ala Gln 280 285 290 295	1158
gtc ctg agg ctg atg cgg atc ttc cgc atc tta aag ctg gcc agg cac Val Leu Arg Leu Met Arg Ile Phe Arg Ile Leu Lys Leu Ala Arg His 300 305 310	1206
tcc act ggc ctc cgc tcc ctg ggg gcc act ttg aaa tac agc tac aaa Ser Thr Gly Leu Arg Ser Leu Gly Ala Thr Leu Lys Tyr Ser Tyr Lys 315 320 325	1254
gaa gta ggg ctg ctc ttg ctc tac ctc tcc gtg ggg att tcc atc ttc	1302

Glu Val Gly Leu Leu Leu Leu Tyr Leu Ser Val Gly Ile Ser Ile Phe	
330 335 340	
tcc gtg gtg gcc tac acc att gaa aag gag gag aac gag ggc ctg gcc	1350
Ser Val Val Ala Tyr Thr Ile Glu Lys Glu Glu Asn Glu Gly Leu Ala	
345 350 355	
acc atc cct gcc tgc tgg tgg tgg gct acc gtc agt atg acc aca gtg	1398
Thr Ile Pro Ala Cys Trp Trp Trp Ala Thr Val Ser Met Thr Thr Val	
360 365 370 375	
ggg tac ggg gat gtg gtc cca ggg acc acg gca gga aag ctg act gcc	1446
Gly Tyr Gly Asp Val Val Pro Gly Thr Thr Ala Gly Lys Leu Thr Ala	
380 385 390	
tct gcc tgc atc ttg gca ggc atc ctc gtg gtg gtc ctg ccc atc acc	1494
Ser Ala Cys Ile Leu Ala Gly Ile Leu Val Val Val Leu Pro Ile Thr	
395 400 405	
ttg atc ttc aat aag ttc tcc cac ttt tac cgg cgc caa aag caa ctt	1542
Leu Ile Phe Asn Lys Phe Ser His Phe Tyr Arg Arg Gln Lys Gln Leu	
410 415 420	
gag agt gcc atg cgc agc tgt gac ttt gga gat gga atg aag gag gtc	1590
Glu Ser Ala Met Arg Ser Cys Asp Phe Gly Asp Gly Met Lys Glu Val	
425 430 435	
cct tcg gtc aat tta agg gac tat tat gcc cat aaa gtt aaa tcc ctt	1638
Pro Ser Val Asn Leu Arg Asp Tyr Tyr Ala His Lys Val Lys Ser Leu	
440 445 450 455	
atg gca agc ctg acg aac atg agc agg agc tca cca agt gaa ctc agt	1686
Met Ala Ser Leu Thr Asn Met Ser Arg Ser Ser Pro Ser Glu Leu Ser	
460 465 470	
tta aat gat tcc cta cgt t agccgggagg acttgctacc ctccacccca	1735
Leu Asn Asp Ser Leu Arg	
475	
cattgctgag ctgcctcttg tgccctctggc acagcccagg caccttatgg ttatggtgta	1795
aggagtatgc ccagcccctg aggggagaga tgcattgggat atgcacccag gtttctttta	1855
cagtttttag aatcgttttt agagggtggg gtgtctgaca ccatgccttt gcacctttcc	1915
atgaaatgac actcactggt ctttgcatcg tgggcataaa atgttcacct tttttccaga	1975
tgagtacacc cagaatgcta atttttctgt ccacgtgtga cgctattcta gtgcttggtg	2035
cccagtactg tctatgagtt gtcgtgctcc tgtttctgag gttgtcgtgt gagttctgta	2095
caaaaagccc ccacaagtcg tccagtagaa atgcatctat gaggtcagca aggatatgat	2155
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tagtttttagt accaaaacaa agagaatgca aagttaagca gacttgacca atgcaagtct	2275
ctaagttggt tttataaatg atctgtagtt ccgtggcttg catgggtgca ccaatcatct	2335
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gttaaaccatg cagtgaagat cgaattttt tcccaagaac agatgtgtta gggagagggg	2455
cttcagctaa atagtccaaa ccctagggtg cttaaagcca agttagtga ggctgagccc	2515
cttggttcac agtcaagcct ccttggttcc taggggtgact gtagagaaat gtatttccgg	2575
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ttttgaaata tttatttttt aagatgttta ggagtaaggc cgtgtgtct tccctcaacta	2695
aaaagaagtt tactgttgta tcgtctccct gaggtgaacg ttgttggtt gctagcaagg	2755
cagtagctta atacttttgt tgcctactct gaaagctcat caatgagagc ccttttattt	2815
ccaagcagaa tttagtcaga taattttgct tctaggatat agtatgttgt atatgatgct	2875
gtgattgccc tggagttcct gcccatgact ggaacctgg tggatatgaa gcatgtactc	2935
aaaatataga cgtgcacgat ggtggtgtgg cttaccacag atggaaacac tgcagttcct	2995
acttgcatc ccactgcctt tcatgggggg tgatgggta gaggccagga gaaaggaaag	3055

agttgtaaaa taaaaaactg ctagttcata aaaaaaaaaa aaaaaaa

3102

<210> 18
 <211> 477
 <212> PRT
 <213> H. sapiens

<400> 18

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 Gly Glu Ile Arg Ile Asn Val Gly Gly Phe Lys Arg Arg Leu Arg Ser
 20 25 30
 His Thr Leu Leu Arg Phe Pro Glu Thr Arg Leu Gly Arg Leu Leu Leu
 35 40 45
 Cys His Ser Arg Glu Ala Ile Leu Glu Leu Cys Asp Asp Tyr Asp Asp
 50 55 60
 Val Gln Arg Glu Phe Tyr Phe Asp Arg Asn Pro Glu Leu Phe Pro Tyr
 65 70 75 80
 Val Leu His Phe Tyr His Thr Gly Lys Leu His Val Met Ala Glu Leu
 85 90 95
 Cys Val Phe Ser Phe Ser Gln Glu Ile Glu Tyr Trp Gly Ile Asn Glu
 100 105 110
 Phe Phe Ile Asp Ser Cys Cys Ser Tyr Ser Tyr His Gly Arg Lys Val
 115 120 125
 Glu Pro Glu Gln Glu Lys Trp Asp Glu Gln Ser Asp Gln Glu Ser Thr
 130 135 140
 Thr Ser Ser Phe Asp Glu Ile Leu Ala Phe Tyr Asn Asp Ala Ser Lys
 145 150 155 160
 Phe Asp Gly Gln Pro Leu Gly Asn Phe Arg Arg Gln Leu Trp Leu Ala
 165 170 175
 Leu Asp Asn Pro Gly Tyr Ser Val Leu Ser Arg Val Phe Ser Ile Leu
 180 185 190
 Ser Ile Leu Val Val Met Gly Ser Ile Ile Thr Met Cys Leu Asn Ser
 195 200 205
 Leu Pro Asp Phe Gln Ile Pro Asp Ser Gln Gly Asn Pro Gly Glu Asp
 210 215 220
 Pro Arg Phe Glu Ile Val Glu His Phe Gly Ile Ala Trp Phe Thr Phe
 225 230 235 240
 Glu Leu Val Ala Arg Phe Ala Val Ala Pro Asp Phe Leu Lys Phe Phe
 245 250 255
 Lys Asn Ala Leu Asn Leu Ile Asp Leu Met Ser Ile Val Pro Phe Tyr
 260 265 270
 Ile Thr Leu Val Val Asn Leu Val Glu Ser Thr Pro Thr Leu Ala
 275 280 285
 Asn Leu Gly Arg Val Ala Gln Val Leu Arg Leu Met Arg Ile Phe Arg
 290 295 300
 Ile Leu Lys Leu Ala Arg His Ser Thr Gly Leu Arg Ser Leu Gly Ala
 305 310 315 320
 Thr Leu Lys Tyr Ser Tyr Lys Glu Val Gly Leu Leu Leu Tyr Leu
 325 330 335
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 Thr Val Ser Met Thr Thr Val Gly Tyr Gly Asp Val Val Pro Gly Thr
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 Leu Asp Thr Ile Ala Thr Arg Phe Asp Gly Thr His Ser Asn Phe Val —
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 Arg Gln Gln Ile Arg Lys Ala Leu Asp Glu His Lys Glu Phe Lys Ala
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 gag ctg atc ctg tac cgg aag agc ggg ctc ccg ttc tgg tgt ctc ctg 578
 Glu Leu Ile Leu Tyr Arg Lys Ser Gly Leu Pro Phe Trp Cys Leu Leu
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 Val Ser His Lys Asp Ile Ser Glu Thr Lys Asn Arg Gly Gly Pro Asp
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His Leu Ser Gly His Leu Gln Lys Gln Pro Lys Gly Lys His Lys Leu			
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Asn Lys Gly Val Phe Gly Glu Lys Pro Asn Leu Pro Glu Tyr Lys Val			
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Val Thr Val Pro Tyr Ser Val Cys Val Ser Thr Ala Arg Glu Pro Ser			
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Phe Ile Leu Asp Ile Val Leu Asn Phe Arg Thr Thr Phe Val Ser Lys			
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Thr Val Arg Leu Leu Arg Leu Leu Arg Leu Leu Pro Arg Leu Asp Arg			
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Tyr Ser Gln Tyr Ser Ala Val Val Leu Thr Leu Leu Met Ala Val Phe			
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Ala Leu Leu Ala His Trp Val Ala Cys Val Trp Phe Tyr Ile Gly Gln			
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35      40      45
Cys Asp Leu Thr Gly Phe Ser Arg Ala Glu Val Met Gln Arg Gly Cys
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Ala Cys Ser Phe Leu Tyr Gly Pro Asp Thr Ser Glu Leu Val Arg Gln
65      70      75      80
Gln Ile Arg Lys Ala Leu Asp Glu His Lys Glu Phe Lys Ala Glu Leu
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Ile Leu Tyr Arg Lys Ser Gly Leu Pro Phe Trp Cys Leu Leu Asp Val
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Ser Gly His Leu Gln Lys Gln Pro Lys Gly Lys His Lys Leu Asn Lys
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Glu Ala Asn Gly Thr Gly Leu Glu Leu Leu Gly Gly Pro Ser Leu Arg
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Leu Thr Thr Leu Thr Arg Tyr Pro Asp Ser Met Leu Gly Ala Met Phe
30 35 40

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45 50 55

gat cga gat gga cct ctt ttc cga tat gtc ctc aac ttc tta aga act 603
Asp Arg Asp Gly Pro Leu Phe Arg Tyr Val Leu Asn Phe Leu Arg Thr
60 65 70

tca gaa ttg acc tta ccg ttg gat ttt aag gaa ttt gat ctg ctt cgg 651
Ser Glu Leu Thr Leu Pro Leu Asp Phe Lys Glu Phe Asp Leu Leu Arg
75 80 85 90

aaa gaa gca gat ttt tac cag att gag ccc ttg att cag tgt ctc aat 699
Lys Glu Ala Asp Phe Tyr Gln Ile Glu Pro Leu Ile Gln Cys Leu Asn
95 100 105

gat cct aag cct ttg tat ccc atg gat act ttt gaa gaa gtt gtg gag 747
Asp Pro Lys Pro Leu Tyr Pro Met Asp Thr Phe Glu Glu Val Val Glu
110 115 120

ctg tct agt act cgg aag ctt tct aag tac tcc aac cca gtg gct gtc 795
Leu Ser Ser Thr Arg Lys Leu Ser Lys Tyr Ser Asn Pro Val Ala Val
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Ile Ile Thr Gln Leu Thr Ile Thr Thr Lys Val His Ser Leu Leu Glu
140 145 150

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Gly Ile Ser Asn Tyr Phe Thr Lys Trp Asn Lys His Met Met Asp Thr
155 160 165 170

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Arg Asp Cys Gln Val Ser Phe Thr Phe Gly Pro Cys Asp Tyr His Gln
175 180 185

gaa gtt tct ctt agg gtc cac ctg atg gaa tac att aca aaa caa ggt 987
Glu Val Ser Leu Arg Val His Leu Met Glu Tyr Ile Thr Lys Gln Gly
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Phe Thr Ile Arg Asn Thr Arg Val His Met Ser Glu Arg Ala Asn

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Glu Asn Thr Val Glu His Asn Trp Thr Phe Cys Arg Leu Ala Arg Lys			
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Thr Asp Asp			
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Pro Asp Ser Met Leu Gly Ala Met Phe Gly Gly Asp Phe Pro Thr Ala			
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 Ile Glu Pro Leu Ile Gln Cys Leu Asn Asp Pro Lys Pro Leu Tyr Pro
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 Met Asp Thr Phe Glu Glu Val Val Glu Leu Ser Ser Thr Arg Lys Leu
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 Val His His Met Ser Glu Arg Ala Asn Glu Asn Thr Val Glu His Asn
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atg act gac cca gtc aca tta aat gta ggt gga cac ttg tat aca acg      162
Met Thr Asp Pro Val Thr Leu Asn Val Gly Gly His Leu Tyr Thr Thr
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tct ctc acc aca ttg acg cgt tac ccg gat tcc atg ctt gga gct atg      210
Ser Leu Thr Thr Leu Thr Arg Tyr Pro Asp Ser Met Leu Gly Ala Met
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Ile Asp Arg Asp Gly Pro Leu Phe Arg Tyr Val Leu Asn Phe Leu Arg
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Thr Ser Glu Leu Thr Leu Pro Leu Asp Phe Lys Glu Phe Asp Leu Leu
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Asn Asp Pro Lys Pro Leu Tyr Pro Met Asp Thr Phe Glu Glu Val Val
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gag ctg tct agt act ccg aag ctt tct aag tac tcc aac cca gtg gct      498
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Glu Gly Ile Ser Asn Tyr Phe Thr Lys Trp Asn Lys His Met Met Asp
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acc aga gac tgc cag gtt tcc ttt act ttt gga ccc tgt gat tat cac      642
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 Lys Thr Asp Asp
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 Ala Arg Asp Pro Gln Gly Asn Tyr Phe Ile Asp Arg Asp Gly Pro Leu
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 Phe Arg Tyr Val Leu Asn Phe Leu Arg Thr Ser Glu Leu Thr Leu Pro
 65 70 75 80
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 85 90 95
 Gln Ile Glu Pro Leu Ile Gln Cys Leu Asn Asp Pro Lys Pro Leu Tyr
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 Pro Met Asp Thr Phe Glu Glu Val Val Glu Leu Ser Ser Thr Arg Lys
 115 120 125
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Val Val Ala Val Tyr Gly Thr Leu Ser Asp Leu Leu Ser Val Ala Ser	
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Leu Ile Asp Asp Ile Ala Leu Ile Arg Asp Asp Asp Val Leu Phe Val	
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Cys Glu Gly Glu Pro Phe Ile Asp Pro Gln Thr Asp Ser Lys Pro Pro	
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Glu Gly Leu Leu Gly Phe His Thr Asp Trp Leu Thr Leu Asn Val Gly	
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Phe Glu Pro Ile Leu Asn Tyr Leu Arg His Gly Gln Leu Ile Val Asn	
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Phe	Ser	Gly	Ala	Asp	Leu	Ser	Arg	Leu	Asp	Leu	Arg	Tyr	Ile	Asn	Phe		
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<211> 389

<212> PRT

<213> H. sapiens

<400> 27

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Ser Lys Leu Gly Ile Lys Ala Thr Ser Val Tyr Asn Gly Lys Gly Gly
35      40      45
Leu Ile Asp Asp Ile Ala Leu Ile Arg Asp Asp Asp Val Leu Phe Val
50      55      60
Cys Glu Gly Glu Pro Phe Ile Asp Pro Gln Thr Asp Ser Lys Pro Pro
65      70      75      80
Glu Gly Leu Leu Gly Phe His Thr Asp Trp Leu Thr Leu Asn Val Gly
85      90      95
Gly Arg Tyr Phe Thr Thr Thr Arg Ser Thr Leu Val Asn Lys Glu Pro
100     105     110
Asp Ser Met Leu Ala His Met Phe Lys Asp Lys Gly Val Trp Gly Asn
115     120     125
Lys Gln Asp His Arg Gly Ala Phe Leu Ile Asp Arg Ser Pro Glu Tyr
130     135     140
Phe Glu Pro Ile Leu Asn Tyr Leu Arg His Gly Gln Leu Ile Val Asn
145     150     155     160
Asp Gly Ile Asn Leu Leu Gly Val Leu Glu Glu Ala Arg Phe Phe Gly
165     170     175
Ile Asp Ser Leu Ile Glu His Leu Glu Val Ala Ile Lys Asn Ser Gln
180     185     190
Pro Pro Glu Asp His Ser Pro Ile Ser Arg Lys Glu Phe Val Arg Phe
195     200     205
Leu Leu Ala Thr Pro Thr Lys Ser Glu Leu Arg Cys Gln Gly Leu Asn
210     215     220
Phe Ser Gly Ala Asp Leu Ser Arg Leu Asp Leu Arg Tyr Ile Asn Phe
225     230     235     240
Lys Met Ala Asn Leu Ser Arg Cys Asn Leu Ala His Ala Asn Leu Cys
245     250     255
Cys Ala Asn Leu Glu Arg Ala Asp Leu Ser Gly Ser Val Leu Asp Cys

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260 265 270
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 305 310 315 320
 Thr Gly Ile Asn Leu Arg Val Ala Thr Leu Lys Asn Ala Lys Leu Lys
 325 330 335
 Asn Cys Asn Leu Arg Gly Ala Thr Leu Ala Gly Thr Asp Leu Glu Asn
 340 345 350
 Cys Asp Leu Ser Gly Cys Asp Leu Gln Glu Ala Asn Leu Arg Gly Ser
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 gcagccggag gcgccagggg aggacagcct ttctgcctc agggagaag agagagacag 360
 actacagtga tggagacca ctatgtgtgc acaagaggct gccatccagt gctggagagg 420
 accgagccgt g atg ctg ggg ttt gcc atg atg ggc ttc tca gtc cta atg 470
 Met Leu Gly Phe Ala Met Met Gly Phe Ser Val Leu Met
 1 5 10
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 Gln Arg Glu Glu Ser Thr Cys Thr Ala Ile His Thr Asp Ile Met Asp
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 gac tgg ctg gac tgt gcc ttc acc tgt ggt gtg cac tgc cac ggt cag 614
 Asp Trp Leu Asp Cys Ala Phe Thr Cys Gly Val His Cys His Gly Gln
 50 55 60
 ggg aag tac ccg tgt ctt cag gtg ttt gtg aac ctc agc cat cca ggt 662
 Gly Lys Tyr Pro Cys Leu Gln Val Phe Val Asn Leu Ser His Pro Gly
 65 70 75
 cag aaa gct ctc cta cat tat aat gaa gag gct gtc cag ata aat ccc 710
 Gln Lys Ala Leu Leu His Tyr Asn Glu Glu Ala Val Gln Ile Asn Pro
 80 85 90
 aag tgc ttt tac aca cct aag tgc cac caa gat aga aat gat ttg ctc 758

Lys Cys Phe Tyr Thr Pro Lys Cys His Gln Asp Arg Asn Asp Leu Leu
 95 100 105
 aac agt gct ctg gac ata aaa gaa ttc ttc gat cac aaa aat gga act 806
 Asn Ser Ala Leu Asp Ile Lys Glu Phe Phe Asp His Lys Asn Gly Thr
 110 115 120 125
 ccc ttt tca tgc ttc tac agt cca gcc agc caa tct gaa gat gtc att 854
 Pro Phe Ser Cys Phe Tyr Ser Pro Ala Ser Gln Ser Glu Asp Val Ile
 130 135 140
 ctt ata aaa aag tat gac caa atg gct atc ttc cac tgt tta ttt tgg 902
 Leu Ile Lys Lys Tyr Asp Gln Met Ala Ile Phe His Cys Leu Phe Trp
 145 150 155
 cct tca ctg act ctg cta ggt ggt gcc ctg att gtt ggc atg gtg aga 950
 Pro Ser Leu Thr Leu Leu Gly Gly Ala Leu Ile Val Gly Met Val Arg
 160 165 170
 tta aca caa cac ctg tcc tta ctg tgt gaa aaa tat agc act gta gtc 998
 Leu Thr Gln His Leu Ser Leu Leu Cys Glu Lys Tyr Ser Thr Val Val
 175 180 185
 aga gat gag gta ggt gga aaa gta cct tat ata gaa cag cat cag ttc 1046
 Arg Asp Glu Val Gly Gly Lys Val Pro Tyr Ile Glu Gln His Gln Phe
 190 195 200 205
 aaa ctg tgc att atg agg agg agc aaa gga aga gca gag aaa tct t 1092
 Lys Leu Cys Ile Met Arg Arg Ser Lys Gly Arg Ala Glu Lys Ser
 210 215 220
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 acccactaga tgtgcacaag aggctgccat ccagtgtctg agaggaccga gccgtg atg 299
 Met
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 ctg ggg ttt gcc atg atg ggc ttc tca gtc cta atg ttc ttc ttg ctc 347
 Leu Gly Phe Ala Met Met Gly Phe Ser Val Leu Met Phe Phe Leu Leu
 5 10 15
 gga aca acc att cta aag cct ttt atg ctc agc att cag aga gaa gaa 395
 Gly Thr Thr Ile Leu Lys Pro Phe Met Leu Ser Ile Gln Arg Glu Glu
 20 25 30

tcg acc tgc act gcc atc cac aca gat atc atg gac gac tgg ctg gac 443
 Ser Thr Cys Thr Ala Ile His Thr Asp Ile Met Asp Asp Trp Leu Asp
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 Cys Ala Phe Thr Cys Gly Val His Cys His Gly Gln Gly Lys Tyr Pro
 50 55 60 65
 tgt ctt cag gtg ttt gtg aac ctc agc cat cca ggt cag aaa gct ctc 539
 Cys Leu Gln Val Phe Val Asn Leu Ser His Pro Gly Gln Lys Ala Leu
 70 75 80
 cta cat tat aat gaa gag gct gtc cag ata aat ccc aag tgc ttt tac 587
 Leu His Tyr Asn Glu Glu Ala Val Gln Ile Asn Pro Lys Cys Phe Tyr
 85 90 95
 aca cct aag tgc cac caa gat aga aat gat ttg ctc aac agt gct ctg 635
 Thr Pro Lys Cys His Gln Asp Arg Asn Asp Leu Leu Asn Ser Ala Leu
 100 105 110
 gac ata aaa gaa ttc ttc gat cac aaa aat gga act ccc ttt tca tgc 683
 Asp Ile Lys Glu Phe Phe Asp His Lys Asn Gly Thr Pro Phe Ser Cys
 115 120 125
 ttc tac agt cca gcc agc caa tct gaa gat gtc att ctt ata aaa aag 731
 Phe Tyr Ser Pro Ala Ser Gln Ser Glu Asp Val Ile Leu Ile Lys Lys
 130 135 140 145
 tat gac caa atg gct atc ttc cac tgt tta ttt tgg cct tca ctg act 779
 Tyr Asp Gln Met Ala Ile Phe His Cys Leu Phe Trp Pro Ser Leu Thr
 150 155 160
 ctg cta ggt ggt gcc ctg att gtt ggc atg gtg aga tta aca caa cac 827
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 165 170 175
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 Leu Ser Leu Leu Cys Glu Lys Tyr Ser Thr Val Val Arg Asp Glu Val
 180 185 190
 ggt gga aaa gta cct tat ata gaa cag cat cag ttc aaa ctg tgc att 923
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 Met Arg Arg Ser Lys Gly Arg Ala Glu Lys Ser
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 35 40 45
 Asp Cys Ala Phe Thr Cys Gly Val His Cys His Gly Gln Gly Lys Tyr
 50 55 60
 Pro Cys Leu Gln Val Phe Val Asn Leu Ser His Pro Gly Gln Lys Ala
 65 70 75 80
 Leu Leu His Tyr Asn Glu Glu Ala Val Gln Ile Asn Pro Lys Cys Phe
 85 90 95
 Tyr Thr Pro Lys Cys His Gln Asp Arg Asn Asp Leu Leu Asn Ser Ala
 100 105 110
 Leu Asp Ile Lys Glu Phe Phe Asp His Lys Asn Gly Thr Pro Phe Ser
 115 120 125
 Cys Phe Tyr Ser Pro Ala Ser Gln Ser Glu Asp Val Ile Leu Ile Lys
 130 135 140
 Lys Tyr Asp Gln Met Ala Ile Phe His Cys Leu Phe Trp Pro Ser Leu
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 165 170 175
 His Leu Ser Leu Leu Cys Glu Lys Tyr Ser Thr Val Val Arg Asp Glu
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 Met Arg Arg
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 ggc gcg ctt ctg gcg ggc gcc ttg gcc gcg tac gcc gcg tac ctg gtg 166
 Gly Ala Leu Leu Ala Gly Ala Leu Ala Ala Tyr Ala Ala Tyr Leu Val
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 ctg ggc gcg ctg ttg gtg gcg cgg ctg gag ggg ccg cac gaa gcc agg 214
 Leu Gly Ala Leu Leu Val Ala Arg Leu Glu Gly Pro His Glu Ala Arg
 20 25 30 35
 ctc cga gcc gag ctg gag acg ctg cgg gcg cag ctg ctt cag cgc agc 262
 Leu Arg Ala Glu Glu Thr Leu Arg Ala Gln Leu Leu Gln Arg Ser
 40 45 50
 ccg tgt gtg gct gcc ccc gcc ctg gac gcc ttc gtg gag cga gtg ctg 310
 Pro Cys Val Ala Ala Pro Ala Leu Asp Ala Phe Val Glu Arg Val Leu
 55 60 65
 gcg gcc gga cgg ctg ggg cgg gtc gtg ctt gct aac gct tcg ggg tcc 358
 Ala Ala Gly Arg Leu Gly Arg Val Val Leu Ala Asn Ala Ser Gly Ser
 70 75 80
 gcc aac gcc tcg gac ccc gcc tgg gac ttc gcc tct gct ctc ttc ttc 406
 Ala Asn Ala Ser Asp Pro Ala Trp Asp Phe Ala Ser Ala Leu Phe Phe
 85 90 95
 gcc agc acg ctg atc acc acc gtg ggc tat ggg tac aca acg cca ctg 454
 Ala Ser Thr Leu Ile Thr Thr Val Gly Tyr Gly Tyr Thr Thr Pro Leu
 100 105 110 115
 act gat gcg ggc aag gcc ttc tcc atc gcc ttt gcg ctc ctg ggc gtg 502
 Thr Asp Ala Gly Lys Ala Phe Ser Ile Ala Phe Ala Leu Leu Gly Val
 120 125 130
 ccg acc acc atg ctg ctg ctg acc gcc tca gcc cag cgc ctg tca ctg 550
 Pro Thr Thr Met Leu Leu Leu Thr Ala Ser Ala Gln Arg Leu Ser Leu
 135 140 145

ctg ctg act cac gtg ccc ctg tct tgg ctg agc atg cgt tgg ggc tgg Leu Leu Thr His Val Pro Leu Ser Trp Leu Ser Met Arg Trp Gly Trp 150 155 160	598
gac ccc cgg cgg gcg gcc tgc tgg cac ttg gtg gcc ctg ttg ggg gtc Asp Pro Arg Arg Ala Ala Cys Trp His Leu Val Ala Leu Leu Gly Val 165 170 175	646
gta gtg acc gtc tgc ttt ctg gtg ccg gct gtg atc ttt gcc cac ctc Val Val Thr Val Cys Phe Leu Val Pro Ala Val Ile Phe Ala His Leu 180 185 190 195	694
gag gag gcc tgg agc ttc ttg gat gcc ttc tac ttc tgc ttt atc tct Glu Glu Ala Trp Ser Phe Leu Asp Ala Phe Tyr Phe Cys Phe Ile Ser 200 205 210	742
ctg tcc acc atc ggc ctg ggc gac tac gtg ccc ggg gag gcc cct ggc Leu Ser Thr Ile Gly Leu Gly Asp Tyr Val Pro Gly Glu Ala Pro Gly 215 220 225	790
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ctg ggc ctg gtg gcc atg gtg ctg gtg ctg cag acc ttc cgc cac gtg Leu Gly Leu Val Ala Met Val Leu Val Leu Gln Thr Phe Arg His Val 245 250 255	886
tcc gac ctc cac ggc ctc acg gag ctc atc ctg ctg ccc cct ccg tgc Ser Asp Leu His Gly Leu Thr Glu Leu Ile Leu Leu Pro Pro Pro Cys 260 265 270 275	934
cct gcc agt ttc aat gcg gat gag gac gat cgg gtg gac atc ctg ggc Pro Ala Ser Phe Asn Ala Asp Glu Asp Asp Arg Val Asp Ile Leu Gly 280 285 290	982
ccc cag ccg gag tgc cac cag caa ctc tct gcc agc tcc cac acc gac Pro Gln Pro Glu Ser His Gln Gln Leu Ser Ala Ser Ser His Thr Asp 295 300 305	1030
tac gct tcc atc ccc agg tag ctg ggg cag cct ctg cca ggc ttg ggt Tyr Ala Ser Ile Pro Arg * Leu Gly Gln Pro Leu Pro Gly Leu Gly 310 315 320	1078
gtg cct ggc ctg gga ctg agg ggt cca ggc gac cag agc tgg ctg tac Val Pro Gly Leu Gly Leu Arg Gly Pro Gly Asp Gln Ser Trp Leu Tyr 325 330 335	1126
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61

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/03826

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : C07H 21/04; C07K 14/705; C12N 15/09, 15/63; C12Q 1/68

US CL : 636/23.1, 24.3; 435/7.2, 69.1, 320.1; 530/350

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 636/23.1, 24.3; 435/7.2, 69.1, 320.1; 530/350

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	PARTISETI, M. et al. Cloning and Characterization of a Novel Human Inward Rectifying Potassium Channel Predominantly Expressed in Small Intestine. FEBS Lett. 1998, Vol. 434, pages 171-176, see entire document.	1-9

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
B earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

28 MAY 1999

Date of mailing of the international search report

07 JUL 1999

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized Officer

NIRMAL S. BASI

Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/03826

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

APS, MEDLINE, JAPIO, BIOSIS, SCISEARCH, WPIDS, GENEMBL, NGENSEQ 34, EST, A-GENESEQ 32, PIR 58, SWISS-PROT 35, SPTREMBL 16.

search terms: potassium channel, K+hnov

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s)1-9, drawn to nucleic acids encoding K+Hnov protein having the amino acid sequence of SEQ ID NO:2, the nucleic acid having the sequence of SEQ ID NO:1, nucleic acids hybridizing to said nucleic acids, expression cassette comprising said nucleic acids, cell comprising said expression cassette, method for producing K+Hnov protein of SEQ ID NO:2 and K+Hnov protein of SEQ ID NO:2.

Group II, claim(s)1-9, drawn to nucleic acids encoding K+Hnov protein having the amino acid sequence of SEQ ID NO:4, the nucleic acid having the sequence of SEQ ID NO:3, nucleic acids hybridizing to said nucleic acids, expression cassette comprising said nucleic acids, cell comprising said expression cassette, method for producing K+Hnov protein of SEQ ID NO:4 and K+Hnov protein of SEQ ID NO:4.

Group III, claim(s)1-9, drawn to nucleic acids encoding K+Hnov protein having the amino acid sequence of SEQ ID NO:6, the nucleic acid having the sequence of SEQ ID NO:5, nucleic acids hybridizing to said nucleic acids, expression cassette comprising said nucleic acids, cell comprising said expression cassette, method for producing K+Hnov protein of SEQ ID NO:6 and K+Hnov protein of SEQ ID NO:6.

Group IV, claim(s)1-9, drawn to nucleic acids encoding K+Hnov protein having the amino acid sequence of SEQ ID NO:8, the nucleic acid having the sequence of SEQ ID NO:7, nucleic acids hybridizing to said nucleic acids, expression cassette comprising said nucleic acids, cell comprising said expression cassette, method for producing K+Hnov protein of SEQ ID NO:8 and K+Hnov protein of SEQ ID NO:8.

Group V, claim(s)1-9, drawn to nucleic acids encoding K+Hnov protein having the amino acid sequence of SEQ ID NO:10, the nucleic acid having the sequence of SEQ ID NO:9, nucleic acids hybridizing to said nucleic acids, expression cassette comprising said nucleic acids, cell comprising said expression cassette, method for producing K+Hnov protein of SEQ ID NO:10 and K+Hnov protein of SEQ ID NO:10.

Group VI, claim(s)1-9, drawn to nucleic acids encoding K+Hnov protein having the amino acid sequence of SEQ ID NO:12, the nucleic acid having the sequence of SEQ ID NO:11, nucleic acids hybridizing to said nucleic acids, expression cassette comprising said nucleic acids, cell comprising said expression cassette, method for producing K+Hnov protein of SEQ ID NO:12 and K+Hnov protein of SEQ ID NO:12.

Group VII, claim(s)1-9, drawn to nucleic acids encoding K+Hnov protein having the amino acid sequence of SEQ ID NO:14, the nucleic acid having the sequence of SEQ ID NO:13, nucleic acids hybridizing to said nucleic acids, expression cassette comprising said nucleic acids, cell comprising said expression cassette, method for producing K+Hnov protein of SEQ ID NO:14 and K+Hnov protein of SEQ ID NO:14.

Group VIII, claim(s)1-9, drawn to nucleic acids encoding K+Hnov protein having the amino acid sequence of SEQ ID NO:16, the nucleic acid having the sequence of SEQ ID NO:15, nucleic acids hybridizing to said nucleic acids, expression cassette comprising said nucleic acids, cell comprising said expression cassette, method for producing K+Hnov protein of SEQ ID NO:16 and K+Hnov protein of SEQ ID NO:16.

Group IX, claim(s)1-9, drawn to nucleic acids encoding K+Hnov protein having the amino acid sequence of SEQ ID NO:18, the nucleic acid having the sequence of SEQ ID NO:17, nucleic acids hybridizing to said nucleic acids, expression cassette comprising said nucleic acids, cell comprising said expression cassette, method for producing K+Hnov protein of SEQ ID NO:18 and K+Hnov protein of SEQ ID NO:18.

Group X, claim(s)1-9, drawn to nucleic acids encoding K+Hnov protein having the amino acid sequence of SEQ ID NO:20, the nucleic acid having the sequence of SEQ ID NO:19, nucleic acids hybridizing to said nucleic acids, expression cassette comprising said nucleic acids, cell comprising said expression cassette, method for producing K+Hnov protein of SEQ ID NO:20 and K+Hnov protein of SEQ ID NO:20.

Group XI, claim(s)1-9, drawn to nucleic acids encoding K+Hnov protein having the amino acid sequence of SEQ ID NO:25, the nucleic acid having the sequence of SEQ ID NO:21-25, nucleic acids hybridizing to said nucleic acids, expression cassette comprising said nucleic acids, cell comprising said expression cassette, method for producing K+Hnov protein of SEQ ID NO:25 and K+Hnov protein of SEQ ID NO:25.

Group XII, claim(s)1-9, drawn to nucleic acids encoding K+Hnov protein having the amino acid sequence of SEQ ID NO:27, the nucleic acid having the sequence of SEQ ID NO:26, nucleic acids hybridizing to said nucleic acids, expression cassette comprising said nucleic acids, cell comprising said expression cassette, method for producing

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/03826

K+Hnov protein of SEQ ID NO:27 and K+Hnov protein of SEQ ID NO:27.

Group XIII, claim(s)1-9, drawn to nucleic acids encoding K+Hnov protein having the amino acid sequence of SEQ ID NO:30, the nucleic acid having the sequence of SEQ ID NO:28-29, nucleic acids hybridizing to said nucleic acids, expression cassette comprising said nucleic acids, cell comprising said expression cassette, method for producing K+Hnov protein of SEQ ID NO:30 and K+Hnov protein of SEQ ID NO:30.

Group XIV, claim(s)1-9, drawn to nucleic acids encoding K+Hnov protein having the amino acid sequence of SEQ ID NO:81, the nucleic acid having the sequence of SEQ ID NO:80, nucleic acids hybridizing to said nucleic acids, expression cassette comprising said nucleic acids, cell comprising said expression cassette, method for producing K+Hnov protein of SEQ ID NO:81 and K+Hnov protein of SEQ ID NO:81.

Group XV, claim(s)1-9, drawn to nucleic acids encoding K+Hnov protein having the amino acid sequence of SEQ ID NO:83, the nucleic acid having the sequence of SEQ ID NO:82, nucleic acids hybridizing to said nucleic acids, expression cassette comprising said nucleic acids, cell comprising said expression cassette, method for producing K+Hnov protein of SEQ ID NO:83 and K+Hnov protein of SEQ ID NO:83.

Group XVI, claim(s)10, drawn to monoclonal antibody that binds to K+Hnov.

Group XVII, claim(s)11-14, drawn to non-human transgenic animal model for K+Hnov.

The inventions listed as Groups I-XVII do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Group I is directed to nucleic acid (SEQ ID NO:1) encoding the K+Hnov protein of SEQ ID NO:2, nucleic acids hybridizing to said nucleic acid, expression cassette comprising said nucleic acid, cell comprising said cassette, method of producing the K+Hnov of SEQ ID NO:2 and the protein of SEQ ID NO:2. The special technical feature is the disclosed nucleic acid of SEQ ID NO:1 encoding the K+Hnov protein of SEQ ID NO:2. The nucleic acids, proteins, antibody and transgenic animal model of Groups II-XVII do not share the special technical feature of Group I wherein the products of said Groups are structurally and functionally different. As shown in Table 1, pages 8-9, the H+Nov proteins of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 25, 27, 30, 81 and 83 are all structurally and functionally different, the nucleic acids encoding said proteins having different chromosome positions.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/03826

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-9, SEQ ID NO:1 and 2

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.